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April, 1956

VOLUME 102 • NUMBER 4

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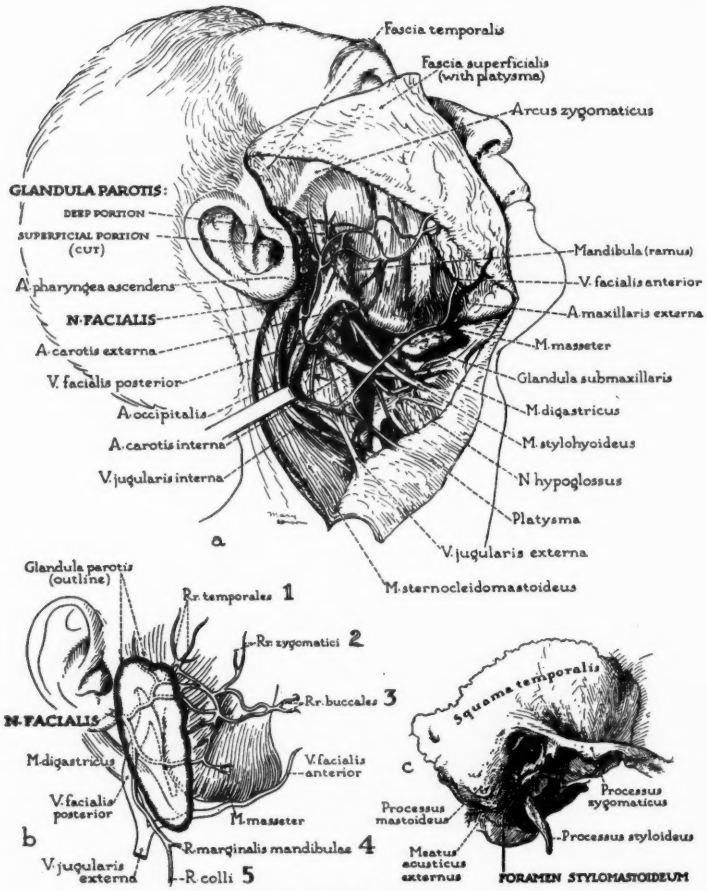

FIG. 1. Parotid gland and facial nerve, together with the vascular, neural, muscular, and skeletal structures related to each. First specimen. a, Structures revealed by reflection of the superficial fascia (with its contained platysma), by retraction of the sternocleidomastoid muscle and posterior facial vein and by excision of the superficial leaf of the parotid gland. The facial nerve emerges from the space between the deep and superficial leaves of the gland (the latter portion cut away). The vagus nerve is indicated by the arrow. b, Facial nerve (same specimen) in relation to the masseter muscle, to the superficial leaf of the parotid gland (outlined), and to the facial tributaries of the external jugular vein. c, Temporal bone, recording in lateral view, the relation of the stylomastoid foramen to the mastoid process, the external acoustic meatus, the styloid process, and the sheath of the latter prominence.

Surgical Anatomy of the Facial Nerve and Parotid Gland Based upon a Study of 350 Cervicofacial Halves.—Richard A. Davis, Barry J. Anson, John M. Budinger, and Le Roy E. Kurth.

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SURGICAL ANATOMY OF THE FACIAL NERVE AND PAROTID GLAND BASED UPON A STUDY OF 350 CERVICOFACIAL HALVES

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THE TASK OF COMPLETE REMOVAL of the parotid gland, in the presence of neoplasms, with preservation of the facial nerve has been vigorously undertaken only within the last three decades. Since the procedure has become common, attention has been focused on the importance of an exacting description of the anatomy of the facial nerve with special reference to its relation to the parotid gland.

Early in the twentieth century it was still the opinion of most surgeons that complete parotidectomy, without irreparable damage to the facial nerve, was a virtual impossibility; as a consequence, they were led to concede that the resulting facial palsy was frequently as distressing as the basic pathology. As Bailey (4) has argued, the glaring inaccuracies and discrepancies of the classical anatomic accounts have served to delay solution of this basic problem.

Contribution No. 619 from the Department of Anatomy, Northwestern University Medical School.
The cost of art work was met, in part, through the use of a fund provided by the Central Bureau of Research of the American Otological Society.

The familiar descriptions portray the gland as being invested completely by a fascial sheath which is continuous with the deep cervical fascia, and having buried inextricably within its parenchyma the divisions and branches of the facial nerve. The parotid space is figured in cross-section diagrams which depict the gland as a single-lobed structure whose posteromedial portion, irregularly wedge-shaped, extends into the retropharyngeal space. The pattern of the parotid duct and its contributory extraglandular "ductules," the plexiform character of the facial nerve, and the bilobed form of the gland are features consistently omitted or inaccurately presented in textbooks of gross and microscopic anatomy.

Luschka, in 1862 and 1867, placed emphasis on the topographic anatomy of the parotid area with details concerning the borders of the gland, surrounding structures (including the blood supply of the region), and the manner in which the facial nerve was thought to run through the substance of the parotid gland. The intertwining and

arciform character of the peripheral distribution of the facial nerve was accounted for in a graphic fashion. In 1867, Quain disposed of the extradural course of the facial nerve with statements that "the gland is also traversed by the facial nerve, which divides into branches within its substance," and that "it is pierced by branches of the great auricular nerve." In 1873, Henle, in an account briefer than Luschka's, stated that the main division of the facial nerve and its lesser branches become imperfectly split between a less bulky deep lobe and a larger superficial lobe. In 1879, Sappey gave a complete account, naming the vascular relations and connections as well as the lymphatic drainage of the parotid area, and referred to the "subparotid plexus," stating that the temporofacial division was the only one which gave off anastomotic branches. In 1898, Poirier added little to Sappey's account, but stated that the nerve, after following a deep course proximally, reached more superficial level near the periphery of the gland. Piersol, in 1930, implied that a partition, continuous with the capsule of the gland, passed through the organ; but the two primary divisions of the nerve were referred to as giving off innumerable branches which subdivided in the parenchyma of the glandular tissue. In 1912, Testut gave a stereotyped description of the nerve in relation to the gland and stated that the branches attained more superficial position as they approached the periphery; the primary divisions were said to be lodged deep in the gland.

It remained for Grégoire, in 1912, to establish the bilobed structure of the parotid gland, and he believed the deep and superficial lobes were joined at the superior border of the gland ($\wedge$-shaped). Furthermore, Grégoire clearly emphasized that the nerve, in its peripheral course, was lodged in a connective tissue plane which separates the two lobes. On the basis of study of 60 adult dissections, the surgical importance of the bilobed character of the gland was stressed. Grégoire referred to Luschka as originally stating that the gland was bilobed in nature. In 1917, McWhorter (33) first directed attention to the complicated character of the tributaries of Stenson's duct, stating that the deep and superficial lobe possessed a main terminal duct which "sometimes receives minor branches from the other lobe." McWhorter restated Grégoire's original thesis, and proved the lobes were joined by an isthmus (H-shaped) to the effect that the facial branches coursed between the two lobes of the gland—sometimes infolded in grooves on the opposing surfaces, but rarely surrounded by glandular parenchyma. McWhorter was unable to find Grégoire's reference to the bilobed character of the parotid gland in Luschka's textbook of anatomy, but noted that this fact was mentioned briefly in Henle. McWhorter's work stands as a significant landmark in the solution of this problem, since his conclusions were based on numerous dissections (66 in number). In 1924, Braus described the nature of "the gland in front of the ear which makes slime" in greater than usual detail. However, despite certain amplification of detail, the parotid plexus was erroneously described as being located deep in the substance of the gland, and no mention was made of the latter's bilobed character. In 1924, Rouvière (42) referred to the temporofacial and cervicofacial divisions of the nerve as taking origin between the two lobes of the gland, to the course of the nerve through a connective tissue plane, and to the separation of the primary divisions by an isthmus. In his volumes on the peripheral and autonomic nervous systems, published in 1927, Hovelacque described the cranial portion of the facial nerve in thorough detail; yet, in dealing with the subject of its peripheral distribution, no mention was made concerning the relation of the nerve to the parotid gland, and the work of Grégoire and that of McWhorter (33) occasioned no comment.

Rouvière and Cordier (43) established the stage in development at which the gland became bilobed, and the embryologic mechanism of origin of the deep lobe of the gland. Human fetuses of 31 and 51 milli-

meters were employed by these authors. In the former stage, the parotid gland extended as far posteriorly as the division of the facial nerve and was entirely superficial to the nerve, which indicated that only the superficial lobe was present at this stage of development. In the 51 millimeter fetus, diverticula of the superficial lobe were observed to pass in the interval between the cervicofacial and temporofacial divisions and to spread out deep to the nerve and its branches. The deep lobe was believed to be of a double origin; as suggested by Grégoire, the superficial lobe is limited in its growth at the superior border by the base of the skull and is deflected inward and downward deep to the nerve. The second mode of origin was advocated by McWhorter, who believed that lobules sank deep in the parotid region and then spread out deep to the main trunk of the nerve. In Tortella's excellent contribution, it is stated that the course of the facial nerve in the parotid area had scarcely interested anatomists. He emphasized the fact that even more recent accounts merely copied original descriptions; these borrowed descriptions treated this complicated problem with such brevity so as to offer a schematized concept of the true relations. Tortella's criticism seems fully justified, when it is discovered that in none of 14 modern textbooks of anatomy (gross and microscopic) does there appear a correct description of the important, closely related, extraglandular tributaries of the parotid duct (most of these standard sources containing no description, either good or bad).

Fundamental to any discussion of the course of the facial nerve is a consideration of the gross constitution of the parotid gland. Quite consistently the textbooks of anatomy describe the gland as if it were a quadrilateral mass, from the deep aspect of which a wedge-shaped portion extends inward toward the pharyngeal wall.

In an earlier article (30) emanating from the present authors' laboratory, the form of the parotid gland received special attention. It was recorded that the gland invariably is a bilobed structure, and that the facial nerve (despite variation in pattern of branching and anastomosis) courses distalward through a cleavage plane which intervenes between a superficial and a deep lobe. This concept of bilaminar character is in agreement with that of Hamilton Bailey (3, 4,5), whose surgical experience had revealed that there is such a definite cleavage plane between the two lobes and that "the facial nerve runs through the parotid gland like meat through a parotid sandwich." McKenzie, using specimens injected with various dyes, concluded that, although the gland possessed deep and superficial "portions," it was not composed of two lobes through which coursed the facial nerve.

Recently Kidd has pointed out that Carwadine was the first surgeon to remove the parotid gland successfully and preserve the facial nerve; although this procedure was carried out in 1907, there is probably a more lively historical background associated with the early surgical attempts to extirpate the diseased parotid gland. In his "Lecture Delivered in Jefferson Medical College, Philadelphia, on the evening of Tuesday the 22nd of January 1833," Pattison discussed this matter fully, and in a classic lecture to his students he made a rebuttal to the statement by the then Professor of Surgery at the University of Pennsylvania, to the effect that the parotid had never been, and never could be, totally removed. Professor Pattison cited a paper by Heister, written in 1733, in which a diseased parotid gland was extirpated. No less than 15 references are given by Pattison to articles published from the year 1733 to 1830 in the French, German, and English surgical and anatomic literature, in which parotid extirpation was not only executed, but practicability of the procedure established. The following pertinent quotation from Professor Pattison's article, concerning early surgical extirpation of the gland, establishes the genesis of the procedure and points to the misconceptions regarding the period in which the procedure was first performed:

"In the 'Archives Generales' for the year 1824, Berard has published a case, in which Beclard, the late distinguished Professor of Anatomy in the Ecole de Medicine at Paris, a man whom we would really suppose knew enough of anatomy to enable him to decide whether the Parotid Gland had or had not been removed, has asserted *positively, after the operation, that it was entirely extirpated.* If a doubt could have remained, as the patient died fifteen days after the performance of the operation, from erysipelas—a disease, which, you are aware, frequently destroys life after the simplest surgical operations performed in the neighbourhood of the head, an opportunity was thus afforded for examining the parts. This dissection was conducted by the Professor of Anatomy in what is acknowledged to be the first Anatomical School in the World, assisted by other eminent Anatomists; and both he and they have certified, that *the entire gland was removed by the operation.*"[1] Pattison further reviewed 3 successful cases of complete surgical removal of the parotid gland performed by George M'Clellan in America between 1826 and 1833.

In spite of such assurances, the renowned surgeon and anatomist Sir Frederick Treves in 1901 stated, "it follows from the complex relations of the parotid that its entire removal as a surgical procedure is an anatomical impossibility." So it should be the cause of small wonder that technical defeatism tinged the predominating philosophy of the early pioneers in surgery of the parotid region. The generalized description of Eisendrath in 1907 to the effect that "the facial nerve divides, inside the gland, into a larger number of branches which perforate the capsule on its anterior and upper borders, forming the pes anserinus" could serve only to perpetuate the inaccuracies which so frequently appeared in the earlier surgical and anatomic literature.

In 1916, Barbat described a method for complete parotidectomy without injury to the facial nerve; dissecting the gland from its inferior border, he isolated the mandibular branch of the nerve, then worked medialward to the main trunk. Barbat's report was based upon a single case, in contrast to the report from the Mayo Clinic by Sistrunk who reviewed 112 cases of surgery on the parotid gland. The procedure of choice included initial isolation of the cervical branch of the facial nerve and subsequent dissection dorsalward through the substance of the gland to the point of division of the trunk into the several rami. No mention was made of the bilobed character of the gland, but the extremely complex pattern of the peripheral portion of the nerve was effectively described. The surgical anatomy text of Corning in 1922 still taught the concepts that total parotidectomy was impossible without damage to the parotid plexus, and that the gland consisted of a single mass of parenchymatous tissue. In 1923, Adson and Ott amplified the work of Sistrunk and described still another surgical anatomic approach to the nerve through the glandular parenchyma: an incision is carried downward from the zygoma, the temporal and cervical divisions of the nerve isolated, the incision then sent forward on the muscles of the face. In 1927, McWhorter (34), in an excellent article, restated his thesis which was presented 10 years earlier; strengthened by additional observations in anatomy and by accumulated experience in surgery, he recorded continuing conviction that the parotid gland is divided into a deep and superficial lobe (connected by an isthmus in its midportion) between which pass the facial nerve with its many branches. On the dissenting side, and as late as 1926, Deaver still held to the belief that removal of the parotid gland must result in facial paralysis; in 1944, Coleman commented on the extreme complexity of the peripheral rami of the nerve (as observed in anatomic dissections) and Malcolm, in 1934, referred to the bilaminar structure of the gland, the connection formed by an isthmus, and the relations of the nerve to the external carotid artery and the poste-

[1]The italicized phrases duplicate those in Professor Pattison's original article.

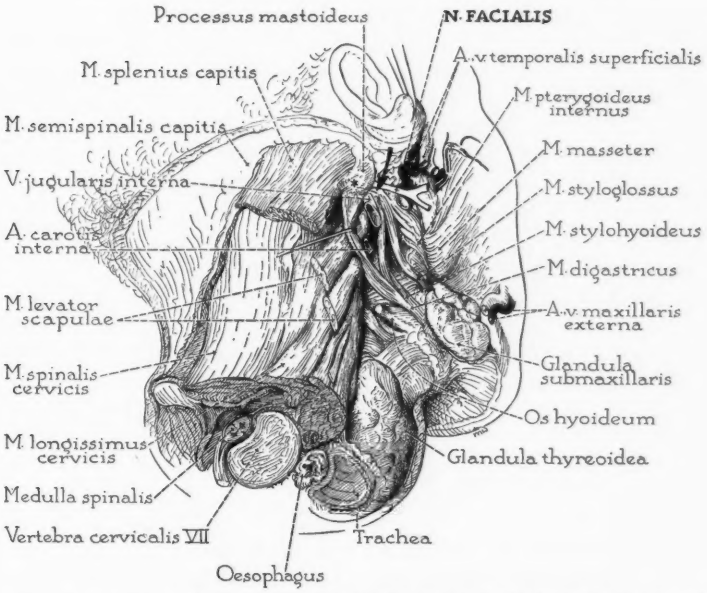

FIG. 2. Structures which form, or are closely related to, the fossa for the parotid gland. Second specimen. The parotid gland has been wholly removed, the sternocleidomastoid muscle cut away from the mastoid process of the temporal bone (at *); the great vessels (together with arterial branches and venous tributaries) have been transected; the facial nerve has been cut just distal to the point at which the trunk divides into temporofacial and cervicofacial portions. Superficially the parotid gland overlapped the masseter muscle in front, the sternocleidomastoid muscle behind. On deeper level it rested upon the styloid group of muscles, the styloid process (at arrow), the internal pterygoid, and digastric muscles. The following neighboring structures are also shown: muscles of the head, neck, and shoulder; hyoid bone; thyroid cartilage; submaxillary gland; mastoid process of the temporal bone.

rior facial vein. However, the nerve was not described as running in an interlobar cleavage plane of connective tissue.

Callander, in 1939, and Beesley and Johnston in 1935, in textbooks which were then standard, adhered to the classical teaching. In 1943, Janes described the facial nerve as being placed between the deep and superficial lobes of the gland. Surgically, Janes approached the trunk of the nerve from below and behind; then, blunt dissection was carried upward, the external carotid artery ligated, and the operation extended toward the periphery of the gland. Dargent and Duroux, in a contribution whose observations were similar to those of McCormack, Cauldwell, and Anson, presented 5 main types of facial nerve distribution; they also described the bilobed constitution of the parotid gland and the presence of a fibrous plane as constant anatomic features. Dissection, which started from the posterior and inferior aspects of the gland, was advocated for the surgeon. State clearly adhered to the general principles of Bailey, McWhorter, and Grégoire, but emphasized the many difficulties encountered when the dissection is begun posteriorly. In his experience the best results were obtained when the procedure was begun at the anterior portion of the gland—to find the cleavage plane between lobes as a guide to the main trunk of the nerve. State emphasized anew that surgical enterprise in the parotid area must not be impeded by dependence upon the older, inaccurate anatomic descriptions. Nelson

and Deeb believed that the high recurrence rate after surgery for removal of parotid tumors could be blamed on the basic misconception that the facial nerve takes its course directly through parotid tissue. In their surgery, governed by the newer concept (in 100 cases presented), the dissection was begun anteriorly; the mandibular division of the facial nerve was then isolated, the posterior portion of the gland isolated, and the main trunk of the nerve identified. Martin (28) would likewise have it that the important consideration in the surgical anatomy of the parotid gland and the facial nerve is the relation of the seventh nerve to the parotid gland. However, he would regard as academic any interest in the thin connective tissue plane which separates the two lobes of the gland because the maneuvers of the surgeon aim solely to keep the nerve uninjured. He advocated that dissection of the gland and nerve be started anteriorly and inferiorly with exposure of the main trunk. In their discussion of the surgical anatomy of the facial nerve, Ariel, Jerome, and Pack have encountered this structure as lying directly within the parotid parenchyma, and the plane of cleavage between the deep and superficial lobes is referred to as a "hypothetical space." It is of considerable interest that these authors quote Rouvière's anatomic account of the parotid lymphatic drainage, which alludes to "the fine cellular tissue which unites the superficial and deep lobes of the parotid gland." It is such liberal interpretation and remarkable contradiction of anatomic relationships which has, coupled with inaccurate text descriptions, led to further confusion of the usual anatomic features in the parotid region.

In presenting their new observations by means of pictorial records of the dissector's experience and by explanatory text based thereon, the authors adhere to the defensible conviction that an increase in detailed information covering anatomic structure in any organ or region of the body will open the way for more meticulous effort—forearmed, surgically, with information gleaned from the laboratory rather than hampered by subservience to archetypal (and hence, ofttimes, fallacious) depiction of human anatomy.

MATERIALS AND METHODS

To the records previously available, those gathered from 250 facial halves were added, to make a total of 350. The specimens were adult whites and negroes (predominantly white males). The authors include in this series only those specimens which were complete in all details affecting the peripheral distribution of the facial nerve and the form of the parotid gland.

As Symington has pointed out, the usual method of dissection of the parotid area has been designed to clarify the deep relations and general form of the gland, and the dissector usually removed the gland piecemeal in an effort to visualize the facial nerve and underlying vascular anatomy. This dissection approach has been scarcely favorable to adequate demonstration of the bilobed character of the parotid gland.

These dissections were planned to show most advantageously the relations between the parotid gland and the facial nerve. First, the skin and superficial fascia were reflected in the parotid region, with subsequent dissection carried from the anterior portion of the gland posteriorly; small peripheral filaments of the nerve were dissected to the anterior border of the parotid gland. Next, the border of the parotid gland was carefully elevated and the rami of the nerves followed posteriorly by blunt dissection between the two lobes. This maneuver carried the dissector to the isthmus of the gland and to the point of bifurcation of the facial trunk. The isthmus was cut and the trunk of the nerve followed to the region of the stylomastoid foramen. Further dissection was carried posteriorly and inferiorly to expose the cervical and mandibular branches of the cervicofacial division.

In some instances a second method was employed, in which the dissection was commenced at the posteroinferior aspect of the

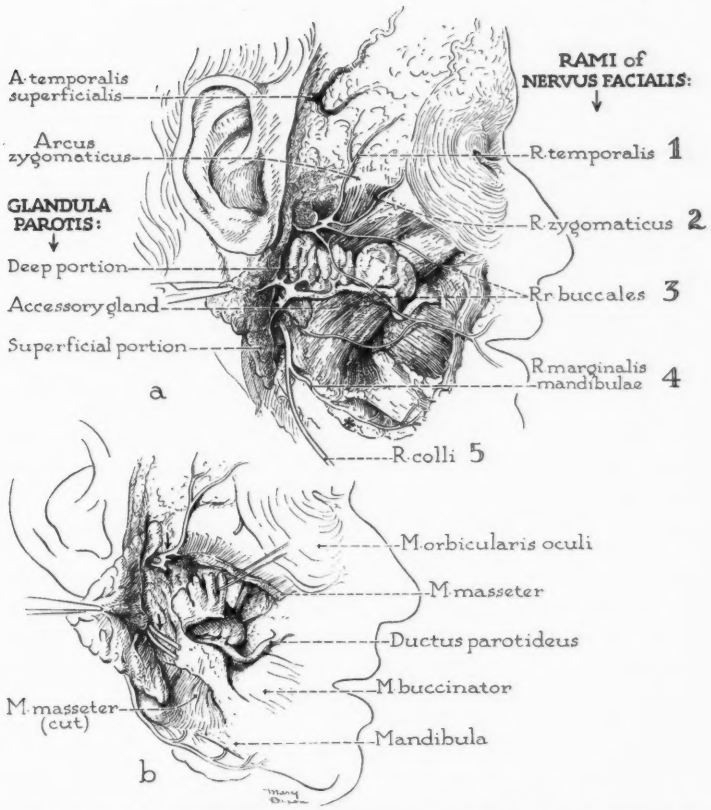

FIG. 3. Facial nerve, parotid gland and duct. Third specimen. a, Temporofacial and cervicofacial divisions of the facial nerve, the five regular branches of the latter, the two-layered parotid gland, and the extraglandular "ductules" tributary to the parotid duct. The superficial portion of the gland, here reflected, covered its deep portion (but not the accessory part), the tributaries of the main duct, and the roots of division of the nerve. The mandibular ramus of the facial nerve crossed the submaxillary gland (at *). b, Anterior part of the superficial leaf of the parotid gland reflected (after cutting the duct) with resultant exposure of the deep portion. The latter occupies the parotid fossa in the area behind the ramus of the mandible. The masseter muscle has been partially excised in order to demonstrate the relation of the gland to the mandible. The temporofacial and cervicofacial divisions of the nerves have been cut (at arrows) near the point where they pass cranial and caudal, respectively, the isthmus of the gland.

superficial lobe, and the cervical and mandibular branches were isolated. Blunt dissection, carried upward and anteriorly, exposed the peripheral branches of the temporofacial division. The dissection was next extended anteriorly, to follow the rami beyond the anterior border of the gland, where they rested on the masseter muscle and ended in the muscles of facial expression.

Detailed individual drawings of the areas were made to show the basic patterns of the facial nerve and the form and dimensions of the parotid gland. In a representative number of specimens the distance from the bifurcation of the facial trunk to the external angle of the mandible was taken, and the height and width of the parotid gland recorded. The character of the venous drain-

age and arterial supply and their relation to the parotid gland was observed in all specimens.

Data on the styloid process and its sheath were secured from specimens in the Department's osteologic collection. Measurements were taken only in those instances in which the process had sustained no injury in the course of preparation. Since there existed no constant similarity between the sides of the same skull, the data presented will not be divided on the basis of lateral halves of the same cranium or on that of sides inclusively.

OBSERVATIONS AND DISCUSSION

Facial Nerve and Parotid Gland

In the adult, the facial nerve comes into relationship with the parotid gland (Figs. 1a, 2, and 5 to 8) immediately upon leaving the stylomastoid foramen (Fig. 1c). Described ordinarily as if it were within the gland, the nerve is said to run in an arciform course which is concave upward and medianward. It passes in front of the posterior belly of the digastric muscle and lateral to the styloid process, the external carotid artery, and the posterior facial vein (Figs. 1a and 4). When the nerve reaches the posterior border of the ramus of the mandible, it turns forward at almost a right angle, breaking up into its terminal branches, which then course to the musculature of facial expression (Figs. 1a, 1b, 3a, and 4 to 8).

This close association of gland and nerve is the result of glandular growth, dorsalward from the mucosal lining of the oral pharynx. The primordium of the gland arises as an epithelial bud, then grows by branching into a brush-like system of solid cords and ducts whose ends form acini. Differentiation of this system occurs, and the ducts become hollow. A dense mass of mesenchyme furnishes an investment and subdivides the gland into lobules. Of the three sets of salivary glands, the parotid is the first to appear, migration posteriorly of the epithelial cells (from the angle of the mouth) beginning in the embryo of 10 millimeters (6 weeks). A tube is formed by a hollowing process; as the island of epithelium grows backward toward the ear, the body of the gland and future duct become differentiated; acinar cells are present at the 5 millimeter stage, but differentiation is not completed until after birth.

Rouvière and Cordier (43) were not entirely satisfied with the earlier accounts of Grégoire and McWhorter (33) regarding the stage in development at which the parotid gland became bilobed. It was pointed out that the fetuses (of 8 cm.), described by Grégoire and by McWhorter (who studied a series of specimens of 36 cm. to 54 cm.) had progressed too far in their development; in their study, 31 and 51 millimeter embryos were used. In the 31 millimeter human embryo, the outline of the parotid gland was found to extend posteriorly to reach the divisions of the facial nerve, and the gland was entirely outside the plane in which the branches of the facial nerve coursed. In the 51 millimeter fetus the parotid gland reached well beyond the point at which the nerve bifurcated so that it covered the trunk over an appreciable fraction of its length, passing at first over and then inward in relation to the trunk. Rouvière and Cordier (43), from an examination of younger reconstructions, concluded that the deep lobe was of double origin, as described first by Grégoire and then McWhorter. Grégoire would have it that the two parotid lobes are joined at their superior borders, and that this relationship was supported, embryologically, by the observation that in the human embryo of 3 months (8 cm.) the parotid gland was found to be entirely superficial to the facial nerve. Then in the fetus of 6 or 7 months, Grégoire observed the primordia of a deep lobe. The adult shape of the gland was considered to be the result of limitation of space: definitive superficial lobe being hindered by the base of the skull, consequent deflection inward and downward produced a deep lobe. According to McWhorter's concept of the origin of the deep lobe, the developing lobules of the superficial lobe penetrate posteriorly, in the form of diverticula, deep to the plane

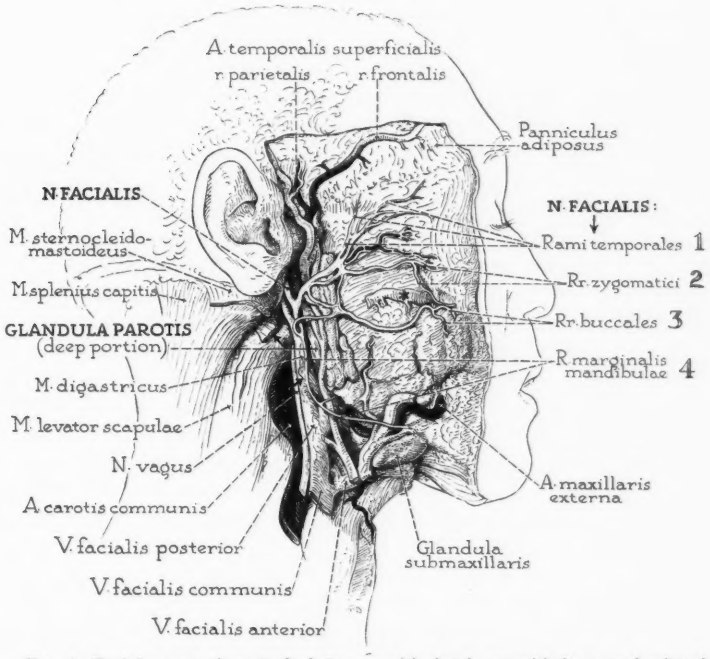

FIG. 4. Facial nerve, deep leaf of the parotid gland, parotid duct, and related blood vessels. Fourth specimen. By removing the platysma and the superficial leaf of the parotid gland, and by excising a segment of the digastric muscle (cut ends at arrows), the following features have been demonstrated: the relation of the trunk of the facial nerve to the mastoid process and to the anterior border of the cranial extremity of the sternocleidomastoid muscle; the relation of the large vessels and of their branches to the portions of the nerve; the pattern of plexiform communication of temporal, zygomatic, and buccal branches; the topography of the deep division of the gland. The distal portion of the parotid duct (at *) remains intact. Inferiorly, the superficial lobe of the gland overlay the cervicofacial division of the nerve, the tributaries of the common facial vein, the common carotid artery and its divisions, and the vagus nerve. Superiorly, the superficial lobe rested upon the temporofacial division of the nerve, and the superficial temporal artery and vein.

of the peripheral branches and the root of the facial nerve.

Important in the present study is the fact that either embryologic description supports the observed bilobed condition in the adult. In fact, in this series of 350 dissections the fundamental adult features are in complete accord with those first described by Grégoire in 1912 and by McWhorter in 1917 and corroborated by Rouvière and Cordier in 1934 and by Tortella in 1935. The more recent surgical accounts by McWhorter (34), Malcolm, Janes, Dargent and Duroux, Bailey (4, 5), State, Nelson and Deeb, and Clarke independently support the basic contention that the parotid gland is composed of two portions, which, in being continuous only along their posterior borders by an isthmus, provide an intervening plane (between superficial and deep laminae) for transmission of the main divisions and peripheral branches of the facial nerve. More recently, Klopp and Winship, McCune, and Clarke have attested to the bilobed nature of the gland and its practicability as a surgical aid and guide in parotid tumor surgery.

The anatomic study by Tortella dealt with the course of the facial nerve in the parotid gland and the character of ramification of the peripheral branches of the nerve.

Tortella objected to the older terminology of "subparotid plexus" of Sappey and Hovelacque and Rauber-Kopsch, and suggested the term "parotid plexus," which described the nerve as being subglandular, interlobular, and intraglandular. Tortella further concluded that the plexiform arrangement of the temporofacial division was formed by dichotic and anastomotic divisions, but that the cervicofacial division was never plexiform in character—being merely a large loop, simple in structure.

Dargent and Duroux[2] followed the organizational pattern of interpretation of their results, as first recorded by McCormack, Cauldwell, and Anson.

Although in 1912 Jefferson and Platt accounted for the relationship between the styloid process, its musculature, and the parotid gland, the course of the facial nerve trunk immediately upon its emergence from the stylomastoid foramen has been neglected by most authors. This study further concluded, "We have nothing to add to the usual accounts of the Facial Nerve traversing the gland." Upon emergence from the stylomastoid foramen, the facial nerve courses inferiorly and anterolaterally, to encounter the parenchyma of the parotid gland (Figs. 2, 3b, 4, and 6). In every instance, in the present authors' total of 350 cervicofacial dissections, the trunk of the nerve separated into two main divisions, the temporofacial and cervicofacial portions (Figs. 1b and 3a). In 61 specimens[3] of the present series the greatest distance above the external angle of the mandible at which this bifurcation occurred was 4.5 centimeters; the shortest distance was 2.5 centimeters; and the average distance was 3.2 centimeters. As McCormack and co-authors pointed out, these measurements converted into gross estimations of surgical value to the surgeon would mean that, "the point of bifurcation of the facial nerve lies posteriorly and slightly medial to the ramus of the mandible and superiorly two thirds of the distance between the external angle of the mandible and the temporomandibular articulation."

In 38 of the 61 facial halves of the current group, the height of the bifurcation of the facial nerve was between 2.6 and 3.5 centimeters above the external angle of the mandible. These observations are in general agreement with those recorded in the earlier series (30). The method of estimating the point of bifurcation of the nerve is simpler than that suggested by Dargent and Duroux, which used the distance from the vertical border of the maxilla (a more difficult method in view of the fact that the muscle, mandible, and soft tissue intervene).

In all instances the temporofacial division was the larger of the two primary divisions. In the proximal part of its course, this division lies between the lobes of the parotid gland, proximal to the point of its separation into branches (Figs. 1a, 3a and 3b, 5, and 6). The cervicofacial division is usually about half the size of the upper division; its branches and anastomoses are far less complex.

The articles by Tortella, Dargent and Duroux, and McCormack, Cauldwell, and Anson offer classifications of the patterns of

[2]Dargent and Duroux measured 27 specimens and recorded the apparent length (that portion visible to the surgeon) of the facial nerve trunk, which averaged 1.3 centimeters. In the article by Dargent and Duroux, the average distance of the bifurcation of the facial nerve trunk from the vertical border of the maxilla was recorded, while McCormack and associates took the distance from the angle of the mandible. Both of these figures are, of course, of service to the surgeon. In describing the morphology of the nerve in the gland, Dargent and Duroux divided the patterns of branching and anastomoses into two great groups: 60 per cent of the specimens were of the type in which no anastomosis occurred between the cervicofacial and temporofacial divisions, and 40 per cent being grouped in the anastomotic class.

The nonanastomotic group contained three types, according to Dargent and Duroux: the classic variety (25 per cent of the total number), in which the temporofacial division was free of anastomoses, and the cervicofacial division contributory to a cluster of anastomotic branches; the kind which lacked a true temporal component and in which the cervical division appeared to be a brush of collaterals out of the two trunks (20 per cent); a third kind (not a distinct type), in which the rami are given off the cervical divisions at right angles to suggest a ladder-like pattern (15 per cent).

The second large class presented by Dargent and Duroux included those specimens in which there existed an anastomosis between the temporofacial and cervicofacial divisions. The authors described two subtypes: one with a long anastomosis (20 per cent of the total number) between the zygomatic branch and the buccal branches; the other with a short (20 per cent) in which short, thick branches, along with numerous connections between the zygomatic and buccal branches, formed a lozenge-shaped loop with a large buccal branch.

[3]In 9 of the 61 specimens, the height above the angle of the mandible was between 2.0 and 2.5 centimeters; in 19, 2.6 to 3.0; in 19, 3.1 to 3.5; in 8, 3.6 to 4.0; and in 6 specimens, between 4.1 and 4.5 centimeters.

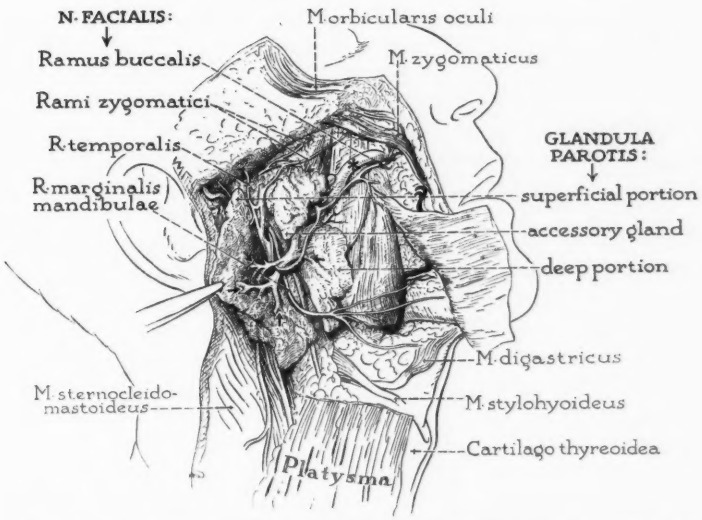

FIG. 5. Facial nerve, parotid gland and duct. Fifth specimen. Removal of the superficial fascia in the region of the face inferior to the zygomatic arch, and retraction of the outer leaf of the parotid gland permit demonstration of the following features: the location of the temporal and zygomatic rami of the facial nerve in the deep substance of the fat-laden superficial fascia (thus near the muscles which they supply); the intimate relation of the several rami to the tributaries (at arrows) of the parotid duct (at *); the manner in which the rami pass to the deep aspect of the layers of facial musculature (see especially the zygomaticus and the platysma); the independence of the accessory lobe of the parotid gland (its ductule being sent into the main duct as a wholly separate unit, the parenchyma being dissociated from the deep lobe); the close relation of the buccal ramus to the parotid duct.

separation of the facial nerve into its peripheral, named, branches. The types of distribution of the nerve presented here follow the same scheme as originally described in the article by McCormack, Cauldwell, and Anson (the basis of cataloging being the degree of complexity attained through anastomosis). Differing relationships between branches of the temporofacial and cervicofacial divisions (temporal, zygomatic, buccal, mandibular, and cervical) resulted in the formation of 6 distinct patterns (Fig. 10). Between the extremes of simplest arrangement and the most complex, were several groups based on the number and character of the anastomosis between the branches of the temporofacial division and the anastomosis between the temporal and cervical divisions.

These statements of general application are based upon careful gross examination of the dissections of the facial nerve. These comments will presently be amplified by a consideration of each of the selected types of neural pattern. However, before proceeding with presentation of the results of this phase of the study, it is necessary to appraise the method employed by comparing the products of its use with those obtained through employment of a far more critical method.

The work of Fujita belongs in the latter category. This investigator used special fixing agents and spent a month on a drawing of a single dissection (in a total of 13 dissections). As a result of exercise of deft skill and artistic portrayal, Fujita traced and pictured elements of a plexus beyond the ken of ordinary naked eye examination. In contrast, the demands which limit identification of structures in the field of a surgical operation render such searching scrutiny impossible; likewise, in everyday laboratory

endeavor, such procedures are impracticable. In both instances, only the major intercommunications are identified—a circumstance which still renders the results of gross anatomic study serviceable to the surgeon.

It now remains to describe the branching patterns and to record the frequency of each of the 6 types.

Type I (44 specimens, incidence of 13 per cent). In the specimens of this group, no anastomoses occur between branches of the facial nerve (Fig. 10, I). The primary division takes place in a dichotic fashion, the branches therefrom then spreading outward like the spokes of a wheel. As might be expected, the temporal branches leave the more superior aspect of the gland and supply the orbicularis oculi and the temporal muscles. The zygomatic ramus follows the parotid duct and is usually superior to it. The buccal supply is more inferiorly placed and its ultimate termination is the region about the mouth.

Type II (71 specimens, incidence of 20 per cent). The distinguishing feature of this type is the presence of an anastomotic connection between the various components of the temporofacial division (Fig. 10, II). The temporofacial division splits into two large portions, one directed transversely, the other anterosuperiorly. The latter ramus then splits into twigs, some of which are directed to the muscles about the eye, while the more inferior branches run directly across the face. These inferior branches anastomose with the main transverse ramus, generally beyond the anterior border of the gland; they give off twigs to the buccal and zygomatic regions. In several instances, the pattern deviated from "type" in that the main anastomosis was established between the zygomatic and temporal rami, the buccal branch coursing alone; in other dissections, there were anastomotic connections between all three rami.

This intimate relation of parotid duct, zygomatic, and buccal branches was observed by Tortella and referred to as the "parastenson anastomosis"; it was stated that its presence was constant. The surgical significance of this arrangement is evident.

Type III (99 specimens, incidence of 28 per cent). This type is an indication of more complex patterns to follow; it is characterized by a single anastomosis between the cervicofacial and temporofacial divisions (Fig. 10, III); the usual scheme is one in which a branch arises from the cervical division immediately distal to the point of bifurcation of the main trunk; this offshoot then follows an oblique course upward to join an arching branch, the zygomatic. The anastomosis occurs beyond the anterior border of the gland and generally over the parotid duct. In all instances, the upward-arching contribution from the cervicofacial division follows either of two schemes: one in which the cervicofacial portion, being of large caliber, supplies the buccal region and sends a relatively small anastomotic branch to the zygomatic ramus; the other is an arrangement whereby the cervicofacial contribution, of small size, after forming a rather large loop, joins the zygomatic ramus—from which anastomosis multiple smaller branches are distributed to zygomatic and buccal regions.

In other variants of the general pattern, all of which were characterized by anastomoses between the temporofacial and cervicofacial divisions, the clinical application is evident; for, as stated by Coleman in his paper on surgical lesions of the facial nerve and the importance of applied anatomy, "because of the plexus-like arrangement of the nerve and the free anastomosis between the branches there may be considerable difference in the effects of a lesion of similar location." Coleman did not attempt to group the various morphologic types of distribution of the facial nerve, but this statement indicated that a more comprehensive anatomic study was warranted to explain rapid return of function or failure in return in those cases in which such restoration could be reasonably expected.

Type IV (82 specimens, incidence of 24 per cent). It is readily seen that this pattern is a combination of types II and III, with an

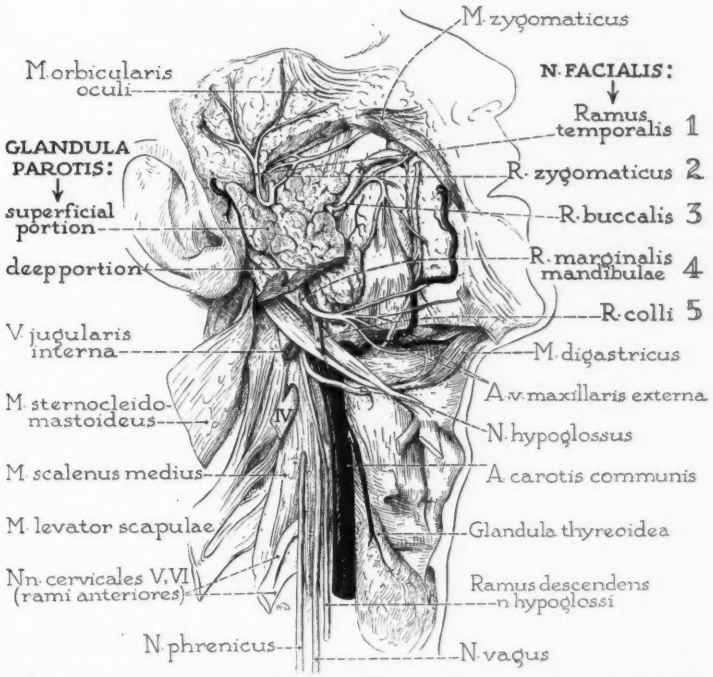

FIG. 6. Facial nerve and parotid gland. Fifth specimen, dissection continued. The superficial lobe of the parotid gland has been restored to its normal position, the lower portion cut away in order to demonstrate the relation of the facial nerve to the cleavage plane which intervenes between the superficial and deep lobes. In the region cranial to the zygomatic arch, fatty tissue has been dissected along the course of the temporal rami of the nerve, in order to make clear the depth at which the nerve branches course in the superficial fascia. The parotid duct is marked by *. In this specimen, as is commonly the case, the five terminal branches of the facial nerve are readily distinguishable. In addition to the temporal rami sent dorsalward to the auricular muscles and ventralward to the muscles of the eyelid, rami pass cranialward to the frontalis portion of the epicranius. Zygomatic branches supply the inferior portion of the orbicularis oculi as well as the zygomaticus. The latter muscle, together with the musculature of the nose and mouth, receive supply from the buccal rami. The marginal mandibular branch sends twigs to the quadratus labii inferioris and to the mentalis. The cervical ramus, covered by the platysma, supplies that muscle.

anastomosis between the temporal and zygomatic branches, as well as connections between the cervicofacial division and the zygomatic or buccal rami (Fig. 10, IV). In addition, a large anastomosis may be established within the temporal component which, lying within glandular boundaries, is sometimes pierced by the posterior facial vein. From the anastomotic loop there arises a group of temporal twigs for the periorbital musculature, and usually a larger single ramus to the zygomatic region.

Type V (32 specimens, incidence of 9 per cent). In this group, there are two anastomotic rami which pass from the cervicofacial division to intertwine with the branches of the temporofacial division (Fig. 10, V). The contribution from the cervicofacial division may be buccal in origin or it may arise from the point at which the main facial trunk divides, then to follow a transverse course on the way to junction with the buccal and zygomatic branches at the periphery of the gland. Those cases in which a transverse

ramus takes origin near the bifurcation of the main facial trunk are so similar to the type III that careful dissection is required to distinguish between the two. The several rami derived from the anastomosis of the two components follow a course cranial to the parotid duct; passing anteriorly across the face, to innervate the musculature between the eye and the mouth.

Type VI (22 specimens, incidence of 6 per cent). This richly plexiform arrangement was encountered least frequently (Fig. 10, VI). Perhaps as a reciprocal, or even dependent, feature, separately large branches are wanting in specimens belonging to this type; small filaments predominate (in contrast to the arrangement in the other types). So prominent is this feature that the transverse branch (which is zygomatic and buccal in distribution) is actually a series of smaller rami and filaments. Within the range of the present study, this pattern represented the most complex pattern of anastomosis; only in specimens of this type does the mandibular branch join any member of the temporofacial division.

It might, a priori, be thought that, since other theoretically possible interconnections actually occur, some specimens of facial nerve might be found in which the cervical branch would send "recurrent" fibers into the face to communicate with the mandibular ramus of the cervicofacial division. None was encountered, possibly because existing fibers would be small and, hence easily destroyed. Were examples of such a complete plexus to be found in subsequent study (to bring all of the five branches into an arrangement of wholly inclusive interchange), the cases would, doubtless, be relative rarities—a belief based upon the observations that connections between the lower (caudal) elements are far less frequent than those among the upper (cranial) branches of the facial nerve (specifically, the mandibular branch communicating with the buccal in only 6.3 per cent of the 350 specimens examined).[4]

[4]Martin (28) was aware of this general circumstance, in stating that surgically the mandibular branch never possesses anastomoses (injury to this branch causing a permanent paralysis of the musculature supplied).

All investigators are not in agreement with the present authors in regard to the gross anatomy of the gland. Thus, although Hurford, stimulated by the work of Bailey, found definite superficial and deep lobes (and in most instances an isthmus), he believed that in only a small percentage of cases did the facial nerve actually follow a course in the connective tissue plane between the two lobes. And, although most of the previous accounts described the superficial lobe as being the larger of the two, Hurford states that in approximately half of his specimens the reverse was true. Hurford's conclusions are at sharp variance with the findings recorded here, since with no exception was the deep lobe ever as expansive as the superficial; and the facial nerve in its peripheral course was always found in the interlobar plane.

McKenzie, in agreement with Hurford, took strong issue with the teachings of Hamilton Bailey (4, 5), namely that the facial nerve rested in the parotid gland like meat in a sandwich. McKenzie attempted to demonstrate that there was no error or omission in the accounts of the textbook accounts in Gray or Cunningham, and that it was Bailey himself who had confused the problem. McKenzie's thesis was that small ducts, indistinguishable from connective tissue, may be present which thus join the two parts of the gland and pass between the small peripheral branches of the facial nerve (at places other than between the two main divisions of the nerve). His conclusions were as follows: there is a deep and superficial "portion" to the gland, not connected by one isthmus, but by many small isthmi; there are many small ducts draining the lobules of the gland deep to the nerve, which empty into a larger duct in the superficial portion of the gland, passing between small peripheral branches of the nerve; the bilobed character is wanting about the region of the nerve trunk. For the concept of a facial nerve lodged, as would be meat in a parotid sandwich, he would substitute one which would liken the gland to a creeping type of plant which entwines itself into the trellis of a fence.

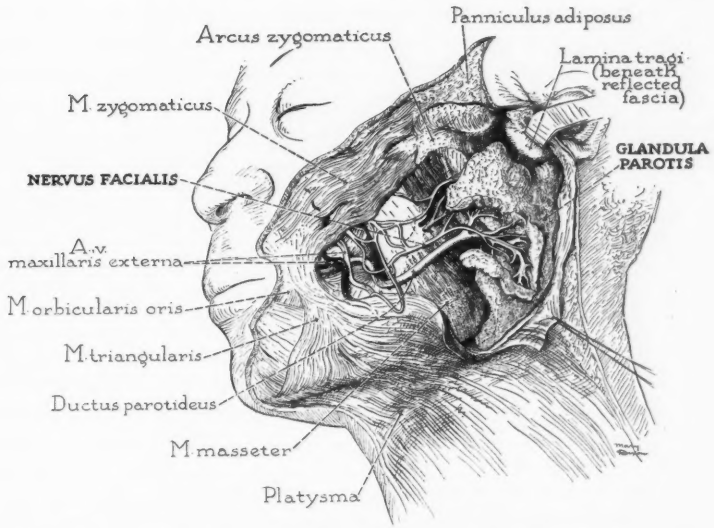

FIG. 7. Facial nerve, parotid gland, parotid duct, and fascia. Sixth specimen. The outer leaf of the parotid gland has been freed and rolled aside along a curving line which, anteriorly, marks that of emergence of the several tributaries of the parotid duct from the parenchyma of the gland. The tributaries and the duct itself are closely related (in the area pictured) to the buccal branch of the facial nerve. A membranous portion of the fascia of the face, together with contained fascicles of the facial musculature, constitutes an outer layer of the "capsule" of the gland. This layer lies just beneath a stratum which may contain a moderate amount of fat (see panniculus adiposus), still present in the dissection, cranial to the zygomatic arch. Over the greater portion of its extent, the parotid gland is covered on its superficial aspect by a membranous layer of fascia, which, not being capsular in the usual sense, merely passes over the triangular area bounded by the sternocleidomastoideus dorsally, by the zygomaticus cranially, and by the platysma and triangularis caudally. Prior to dissection, that is, in the natural state, this fascial layer covered the area which is bounded by the muscles named, enclosed them as it reached their free margins. On the deep aspect the gland rested mainly on the masseter fascia (this layer removed in the dissection).

McKenzie's viewpoint is weakened by his admission that there is an isthmus, since the mere presence of such a connection makes it morphologically necessary for a cleavage plane to exist between the two lobes of the gland. The degree of separation between the two lobes, then, becomes a matter of degree; if grossly, the separation is readily evident and easily found, the gland consists of two "portions or parts" as advocated by McKenzie. The problem resolves itself, using this type of reasoning, into one of semantics rather than morphology.

As will become apparent, the present authors support the concept so well expressed by Bailey (5): "although there are considerable variations in the disposition of the nerve within the gland, for practical purposes it may be stated that much more often than not, the facial nerve lies between a comparatively large superficial lobe and a variably sized deep lobe, the two being connected by an isthmus. It is this general anatomical concept that the operation of superficial lobectomy and complete parotidectomy are rendered practicable."

These and other related facts will be presented, following the review of certain general features pertinent to the present authors' observations.

The parotid gland (glandula parotis) lies upon the side of the face just below and in

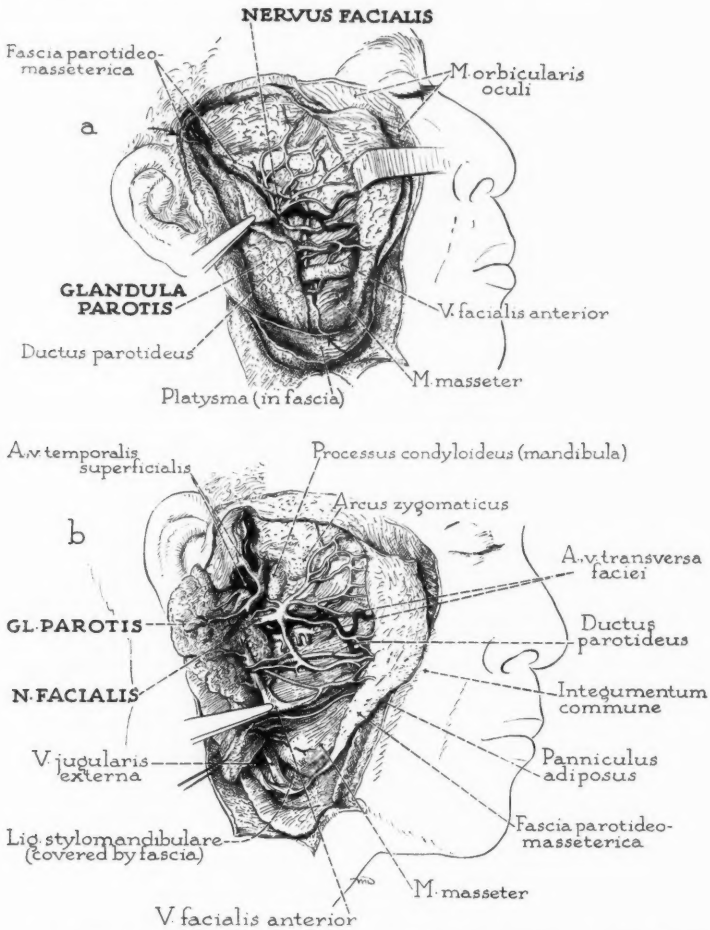

FIG. 8. Facial nerve, parotid gland and duct, investing fascia, and related blood vessels. Seventh specimen. a, Demonstrating that immediately beneath a superficial layer of fascia (the panniculus adiposus) is situated a membranous stratum, which divides to enclose the parotid gland. The external part of the nonfatty stratum contains the muscles of facial expression; the internal lamina covers the muscles of mastication (in this area, the masseter muscle). The laminae join at the periphery of the gland (at large arrows). The envelope thus formed is perforated by the branches of the facial nerve (at small arrows). b, Facial nerve and its branches shown by reflecting the superficial leaf of the parotid gland. Large blood vessels course through the connective tissue which intervenes between the lobes of the gland. The larger vessels are related to the substance of the gland itself only insofar as arterial branches are sent into the gland or venous tributaries are received therefrom, that is, they are not, themselves, buried in the parenchyma of the gland. Here, as is commonly the case, the facial nerve is plexiform. The superficial leaf of this gland in this specimen is of maximal dimensions. The deep leaf is virtually confined to the parotid fossa (that is, to the space for which the mandible serves as anterior boundary).

front of the external ear (Figs. 1b, 6, 7, and 8a). The bulk of the superficial portion (or leaf) which makes up the greater fraction of the gland is situated between the ramus of the mandible anteriorly and the mastoid process and sternocleidomastoideus muscle posteriorly; the gland, however, usually extends beyond these landmarks, in front and behind, overlapping both process and muscle (Figs. 7, 8a, and 8b).

In describing the anatomic form of the parotid gland, Parsons concluded that it was usually the shape of an inverted triangle; however, not infrequently this portion assumes the form of an irregular oval (Figs. 1b and 8a); superiorly, its border almost reaches the zygomatic arch; posteriorly and inferiorly, the base overlaps the sternocleidomastoideus muscle; anteriorly, the apex extends over the masseter muscle, frequently prolonged along the horizontal course of the parotid duct (Figs. 3a and 6). Extending even farther forward, sometimes beyond the masseter muscle to rest upon the buccinator, an accessory glandular mass (glandula parotis accessoria) may occur (Figs. 3a and 3b).

The deep portion of the gland, almost always concealed by the flatter and larger superficial portion, and connected with the former by a broad isthmus, extends inward (medialward) behind the mandible, toward, or even to, the pharyngeal wall (Figs. 1a, 2, 4, 5, and 6).

Considered as a whole, but without inclusion of the inconstant accessory portion, the shape of the parotid gland is that of a three-sided wedge. This means that the gland possesses three surfaces, namely, lateral, anterior, and posterior.

The superficial, or lateral, surface, which is the external part of the superficial leaf of the gland, is the portion which has already been described as commonly being triangular in outline (Figs. 3a, 6, and 7). The posterior border reaches the external acoustic meatus and the sternocleidomastoideus muscle and extends inferiorly to the angle of the mandible and the posterior belly of the digastric muscle. The superior border lies below the zygomatic arch, generally matching the horizontal plane of the arch. The anterior border ascends irregularly to meet the superior border, thus forming the apex of the gland. The apex, directed forward, rests upon the masseter muscle and, when prolonged as an accessory lobe, may follow the duct to the buccinator muscle (Fig. 3a). The duct usually issues from the apical part of the gland. In some cases, the gland may be so large that its superficial surface descends to cover the digastric muscle and below the angle of the mandible, to come into close relation with the posterior part of the submaxillary gland (Figs. 1a, 2, and 4).

The anterior (or anteroinferior) surface of the gland is molded around the posterior border of the ramus of the mandible and the muscles which clothe the latter—the masseter laterally, the pterygoideus internus medially (Figs. 2 and 3). The sulcus thereby produced in the anterior surface of the gland being, in some instances, a deep incisure may continue posteriorly as the cleavage plane between the superficial and deep leaves.

The posterior (or posteromedial) surface is in contact with the sternocleidomastoideus muscle, the mastoid process of the temporal bone, the cartilage of the external acoustic meatus, the posterior belly of the digastricus muscle, the internal carotid artery, the internal jugular vein, the root of the styloid process, and the muscles (stylohyoideus, styloglossus) attached thereto (Figs. 1a, 2, 4, and 6). As the anterior posterior surfaces of the gland meet, the part of the gland thus formed may extend medialward beyond the styloid process, toward the pharynx (Fig. 2); this medial part, the processus retromandibularis, may constitute the bulk of the deep leaf (Fig. 2).

Vessels and nerves which are intimately related to the parotid gland are conventionally described as if they traversed its substance. It is said that the external carotid artery, lying first in a groove on the deep surface of the gland, enters the latter to lie deeply in it as far as the neck of the mandible, there dividing into the terminal branches.

The superficial temporal artery is described as emerging from the upper border of the gland, and the maxillary artery as turning medially and emerging from the deep part of the anterior surface. The transverse facial artery is said to be given off in the substance of the gland, to emerge therefrom between the zygomatic arch and the duct. The posterior facial vein "descends in the substance of the gland" (to quote a familiar source) and divides into the two terminal branches which then emerge from the lower end of the gland. The facial nerve is said to enter the posterior surface of the gland slightly below its middle, to run laterally and forward and to divide into terminal branches "which radiate through the gland" superficial to the external carotid artery and the posterior facial vein. Communicating branches to the facial from the auriculotemporal and great auricular nerves "also traverse the gland substance."

Most of the familiar accounts agree that the recess occupied by the parotid gland is lined by a layer of fascia which is continuous with the deep cervical fascia. The fascia is described as having an attachment superiorly to the zygomatic arch; posteriorly to the external acoustic meatus and the anterior border of the sternocleidomastoideus muscle; medially to the styloid process of the temporal bone; anteriorly it passes over the masseter muscle and blends with the buccopharyngeal fascia. With the periosteum of the tympanic plate, the fascia would thus form a definite sheath for complete investment of the gland. It is said that the anteroinferior part of the sheath, thickened and flattened, becomes the stylomandibular ligament, which passes inferiorly and laterally from the styloid process to the angle of the mandible. In being so disposed, this part of the sheath would separate the anterior part of the parotid gland from the posterior part of the submaxillary gland.

The parotid duct (ductus parotideus stenonis) leaves the upper portion of the anterior border of the gland (Fig. 6). The duct runs in an approximately horizontal plane, forward upon the outer surface of the masseter muscle (Figs. 3a, 5, 6, and 7); it is accompanied by branches of the facial nerve and the transverse facial artery, the latter an appreciable distance superior to the duct. Reaching the anterior border of the muscle, the duct turns sharply medianward, coursing at almost a right angle to its first part as it passes through the fat of the cheek to reach the buccinator muscle (Fig. 3a). Perforating the muscle of the cheek, the duct finally passes for a short distance between the buccinator and the oral mucous membrane, to open into the vestibule of the mouth opposite the second upper molar tooth.

For the requirements of an introductory account, all textbook material just presented seems adequate in respect to features dealing with size, form, and relations of the parotid gland and of its duct. Yet, for the more critical needs of surgery in the region of the face, some aspects of these descriptions are too generalized (seemingly based upon the morphology of an "idealized" gland), while others, oddly, err in the direction of overemphasis on points difficult of demonstration, even in the meticulously dissected specimen. As a consequence, correction or amplification is needed on the following points: dimensions of the gland and the relative bulk of superficial and deep portions; nature of the interlaminar "cleft" which separates the two portions; occupants of this plane between lobes; the nature and position of masses of accessory glandular tissue; patterns of parenchymal origin and extraglandular course of "ductules" tributary to the parotid duct; the local character and peripheral continuities of the gland's fibrous investment; the variability of such an important and guiding landmark as the styloid process of the temporal bone.

The results of examination of specimens of parotid gland in the current series serve to strengthen the conclusion of McCormack, Cauldwell, and Anson concerning variability of the parotid gland in respect to form and size. In complete dissections of 62 consecutive specimens, it was found that the greatest

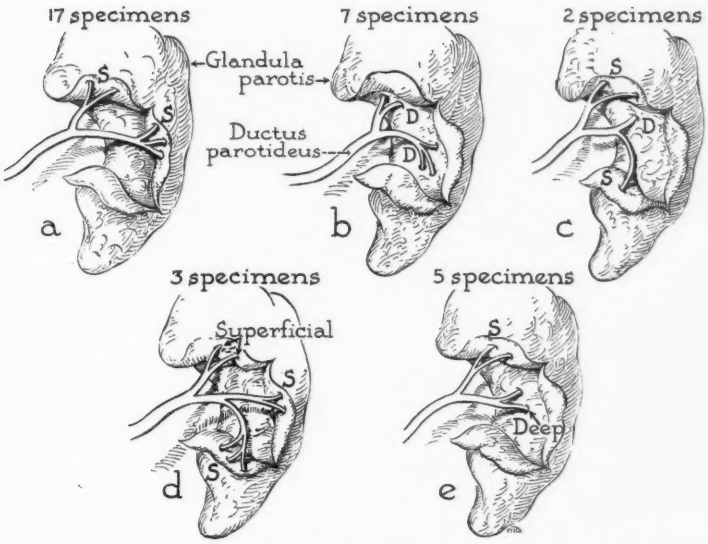

FIG. 9. Types of tributary duct patterns of the parotid duct, from a study of 34 consecutive specimens. Semischematic. The tributaries may arise only from the superficial lobe (Figs. a and d at *S*), from the deep lobe (Fig b at *D*) or from both (Figs. c and e). a, Origin from the superficial leaf only (upper portion and midportion). b, From the deep leaf only. c, From the upper (cranial) and lower (caudal) portions of the superficial leaf, and from the midportion of the deep leaf. d, From the superficial leaf, in the latter's upper, middle, and lower portions. e, From the superficial leaf above and the deep leaf below.

height of the parotid gland was 7.7 centimeters, while the least figure was found to be 4 centimeters; the average height was 5.8 centimeters. In this series, the width of the parotid gland varied from the maximum of 6.5 centimeters to a minimum of 2.0 centimeters. The average width of the gland was 3.4 centimeters.

In the earlier series of measurements (on 76 glands), to which reference has just been made, the length of gland varied between 4.5 and 9.2 centimeters (average, 6 cm.), while the width varied between 2 and 5.4 centimeters (average 3.3 cm.). The larger glands (those longer than 6 cm.) extend for a distance of several centimeters into the neck just anterior to the ventral border of the sternocleidomastoid muscle—a fact which is of surgical interest.

More than half of the glands (40 specimens, or 52.6 per cent) fell into a group for which a conventional textbook description would be suitable; many were triangular in shape, largest at the superior extremity, and narrowing gradually to a blunt apex pointing inferiorly (as in Figs. 3a and 7). In a second group (24 glands, or 31.5 per cent of the total), the gland was not constricted below, but maintained uniform width throughout its length, with superior and inferior poles gently rounded (as in Figs. 1b and 8a). In a third group (6 specimens) the glands possessed the form of an inverted letter L. The average length of these was 5.7 centimeters, while the average width was 4.7 centimeters. The transverse portion of the inverted L, represented by the superior portion of the gland, was made up of glandular tissue which lay along the superior border of the main parotid duct (in 1 instance reaching a length of 5.4 cm.). In the fourth and last category (6 specimens), all of the glands were large, with an average length of 6.7 centimeters, and an average width of 3.7 centimeters. These

glands were roughly triangular in outline, but the broad base of the gland formed the inferior pole of the gland, the superior pole then being represented by the rather sharp apex.

Observations on form (of 100 glands) in the current series were in general accord with those just described, as were also those dealing with dimensions (taken of the glands, in situ): height varied between the extremes of 8.0 and 3.9 centimeters (average 6.0 cm.), while width varied between 6.5 and 2.0 centimeters (average, 3.6 cm.).[5]

In the earlier series, accessory glandular masses were found to be fairly common; 16 such nodules of tissue occurred in 15 of the 76 cases (19.7 per cent). They were invariably situated superior to the main parotid duct, sometimes partially overlapping it (Fig. 3a). In length the accessory glands varied from 1.0 to 2.3 centimeters (average, 1.4 cm.); in width, from 0.5 to 0.8 centimeter (average, 0.7 cm.). The long axis corresponded to that of the main duct, into which the accessory element emptied by a very short, slender duct (Fig. 3a).

In not 1 of 10 familiar textbooks of anatomy (gross and microscopic) is there to be found a correct description of the extraglandular ducts contributory to the formation of the main parotid duct; in several, there is no description at all.

Dissections by McWhorter (33) improved on Grégoire's observations but were in essential agreement with them on basic points. McWhorter was led to believe that the main duct of the gland was closely associated with the superficial lobe than with the deep, and that the plan of branching followed no particular pattern. He stated that each lobe of the gland was drained by a main branch of terminal duct, which often received branches from the other lobe. Frequently, ducts were found which drained a portion of the superficial or deep lobes which crossed in the region of the isthmus to join the duct from the opposite lobe.

[5]Not included in this measured set are the 2 glands pictured in Figures 7 and 8. Each of these was 9.0 centimeters in length, close to maximum for a combined total of 164 parotid glands.

In a series of the present authors' dissections, "ductules" were multiple in every one of 34 specimens (Figs. 9a to 9e). They arose in the following ways: from the superficial leaf only, in its upper and middle portions (Fig. 9a); from the deep leaf only (Fig. 9b); from the superficial leaf (above and below) and from the deep leaf in its midportion (Fig. 9c); from the superficial leaf only, in its upper, middle, and lower parts (Fig. 9d); from the superficial leaf in its upper third and from the deep leaf in its middle third (Fig. 9e). These sources may be summarized as follows: the superficial leaf only in 20 instances (as in Figs. 9a and 9d); from the deep leaf only in 7 (as in Fig. 9b); from both laminae in 7 (as in Figs. 9c and 9e). Put in another way, ductules arose from the superficial leaf or from the superficial and deep leaves in 27 of the 34 cases; and from the deep leaf only in the remaining 7 (a proportion of approximately 4 to 1).

Generally, the contributory elements were short, converging quickly upon a main channel (Figs. 3a, 5, and 7). In some instances, their relation to the nerve was intimate and complex (Figs. 5a and 7).

Structures Related to Gland and Nerve

Blood vessels and nerves. Since anatomic accounts of the bilaminar structure of the parotid gland are relatively recent additions to the literature, it is little wonder that the reader fails to find a modern description in those textbooks upon which he is accustomed to depend for anatomic guidance. Dargent and Duroux attempted to schematize the venous drainage about the parotid gland but came to the conclusion that venous patterns were consistent only in their variations, whereas the small arterial trunks were relatively fixed in their course.

While it is true that relationships of vascular channels are of such character that allocation to types is often impossible, the less accurate kind of observation may be of some service. Dissections have demonstrated that in the region of the inferior extremity of the parotid gland, the anterior facial vein quite

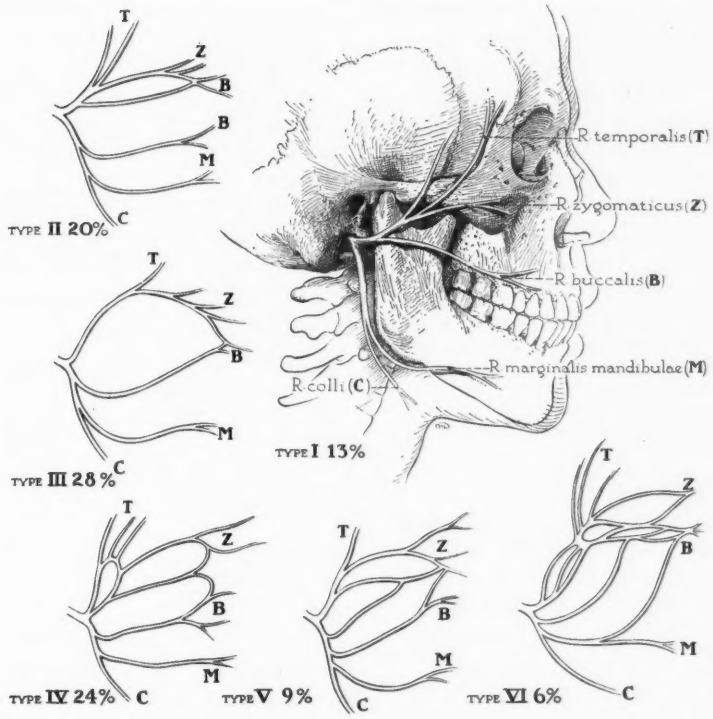

FIG. 10. Chief types of branching encountered in 350 cervicofacial halves. Schematically shown, as of the right side of the head. Note that Types III, IV, V, and VI together represent almost 70 per cent of specimens. Type I, Absence of anastomosis between the branches of the two divisions (temporofacial and cervicofacial) of the facial nerve; although, regularly pictured, actually a least common type. Type II, Anastomoses within the temporofacial division. Type III, Anastomosis between chief divisions. Type IV, Two anastomotic loops within the temporofacial part. Type V, Two loops from the cervicofacial division, intertwined with branches of the temporofacial. Type VI, Extensive intermixture.

regularly courses along the margin of the mandible posterior to the branches of the facial nerve, and then joins the posterior facial vein (Figs. 1a and 4). The latter structure was frequently split by the trunk of the facial nerve, or by the temporofacial division of the latter. The posterior facial vein is generally posterior to the gland or is covered by the superficial parotid lobe. Usually a large retrocondylar tributary of the posterior facial vein courses deep to the ramus of the mandible. The venous channels which are situated between the two leaves of the gland are small and plexiform; receiving tributaries from the parenchyma of the lobes between which they pass, the channels formed by them are directed across the masseteric fascia, following no fixed pattern.

The transverse facial artery, and its accompanying vein, run forward beneath the superficial lobe just inferior to the zygomatic process (Fig. 8b). The external carotid artery courses deep within, or beneath the parotid gland in its superior and medial aspect. Both of these vessels give off fine arterial patterns which pass between, and supply, the two lobes. Although far from constant, the arterial plan is less varied than the venous.

Styloid process. Often useful in preliminary examination of a region of prospective sur-

gery is the presence of a constant skeletal landmark. The styloid process would seem to be a good morphologic candidate for such an office, since it is traditionally pictured as a well developed feature of the normal skull.

Actually, this osseous spine is undependable in the capacity named, since it was not only wholly absent in 58 of 150 cranial halves examined, but shielded by the vagina processus styloidei in more than 20 others—a length of approximately 1 centimeter often being required to bring the process downward beyond the free edge of the sheath. The distribution is as follows: absence, 58; length from 0.1 to 0.9 centimeter, 18 processes; length from 1.0 to 1.9 centimeters, 40; from 2.0 to 2.9, 19; from 3.0 to 3.9, 14; from 4.0 to 4.2 (maximum length), 1 process. It is, perhaps, important to add that bilateral dissimilarity is the rule in the matter of length. In respect to absence, it may be recorded that in 18 skulls total absence was unilateral, while in 20 the styloid process was wanting on both sides.

At this point, references to pictorial records of actual specimens may be serviceable. A styloid process is absent in the skull shown in Figures 11a and 11b; in Figure 1c the process extends for a distance of 1 centimeter beyond the free edge of the vagina processus styloidei (indicated by arrow); in Figure 11d, for a distance of 4 centimeters beyond the sheath. In the specimen shown in Figure 11e the process extends slightly beyond the free border of the vagina processus styloidei; in Figure 11f, a shorter process remains concealed behind the sheath. Figure 12a shows a specimen in which a spur, prolonged from the vagina processus styloidei, simulated a true styloid process (as also in Fig. 11a). The projection in Figure 12b is a true process, but one small in size (1 cm. in length). In Figures 12c and 12d the processes were of medium length (2 cm. and 2.5 cm., respectively). Figure 12e depicts a styloid process of greater than average length; Figures 12f and 12g, an example of an elongate process (two views of the same skull). The examples shown in Figures 12h and 12i were 3.6 centimeters in length, approaching the maximum length of 4.2 centimeters for the series of specimens studied.

Fascia. As previously mentioned, the parotid gland is traditionally credited with the possession of a very distinct fascial investment.

Accounts agree in stating that the investment is continuous with the deep cervical fascia. The dissector and the surgeon are prepared to encounter a covering of capsular intimacy and strength, since it is described as a "definite sheath" which completely encloses the gland, as a "strong fibrous envelope," and as a "capsule" whose superficial portion "is dense and closely adherent to the gland." While it is true that the gland is related to layers of connective tissue which fuse peripherally to enclose it, some qualifying statements are most certainly required.

The outer lamina of the "sheath" is nothing more than the layer of fascia which, in the cervical and lower facial regions, contains the platysma (Figs. 7, 8a, and 8b). In the authors' laboratory experience, the layer is not a locally prominent entity, densely fibrous and closely adherent to the gland; rather (basing a judgment on both routine and special dissections), it is connected to the gland by numerous septa sent inward among the lobules of the gland, with strength little greater than that possessed by coverings of the other salivary glands.

The inner lamina could be regarded as the investing fascia of the masseter muscle since, when freed, the muscle fibers are laid bare. When exceptional care is exercised, it is possible to discover a stripe of fusion between these two layers along the border of the gland (Fig. 8a)—the application of one to the other representing the relationship which ordinarily exists between a superficial and a deep fascia (or muscle fascia) wherever such laminae are not kept apart by the intervening presence of viscera.

The cleavage plane between the superficial and deep portions of the gland is that part of the general connective tissue which, developmentally, was enclosed by the lam-

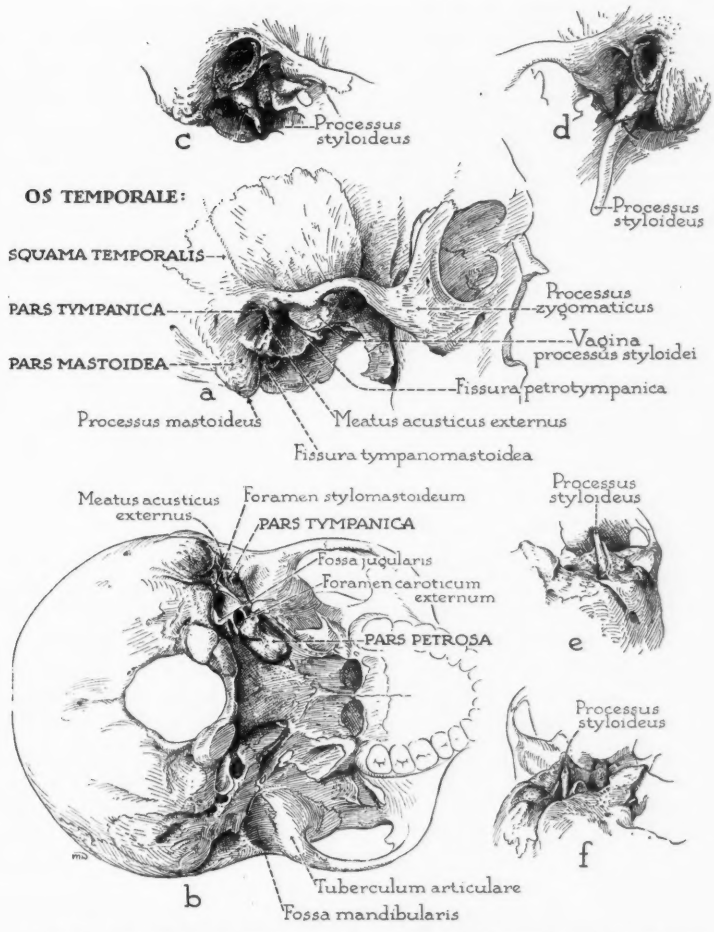

FIG. 11. Skeletal variations in the region of the styloid process and the stylomastoid foramen. a and b, Adult skulls in lateral and inferior views; c and d, adult specimens in lateral view, right and left sides, respectively. e and f, Skull of adolescent, left and right sides, respectively. In a and b a styloid process is wanting. In c the process extends for a distance of 1 centimeter beyond the free edge of the vagina processus styloidei (indicated by arrow); in d, for a distance of 4 centimeters beyond the sheath. In the specimen shown in Figure e the process extends slightly beyond the free border of the vagina processus styloidei; in f, a shorter process remains concealed behind the sheath.

inae as these lobe-like masses twist about the facial nerve and are prolonged ventralward (remaining connected dorsally by the lobules which form the isthmus). The tissue, for purposes of convenient—albeit uncritical—description, could be considered an inward-directed septal derivative of a surrounding "capsule."

SURGICAL COMMENTARY

The clinical experience of Sistrunk with 112 cases of parotid tumors suggested that the anatomic dissection of the gland at surgery be most effectually performed by first isolating the cervical branch, then dissecting upward and following its course through the gland to the point of bifurcation of the facial

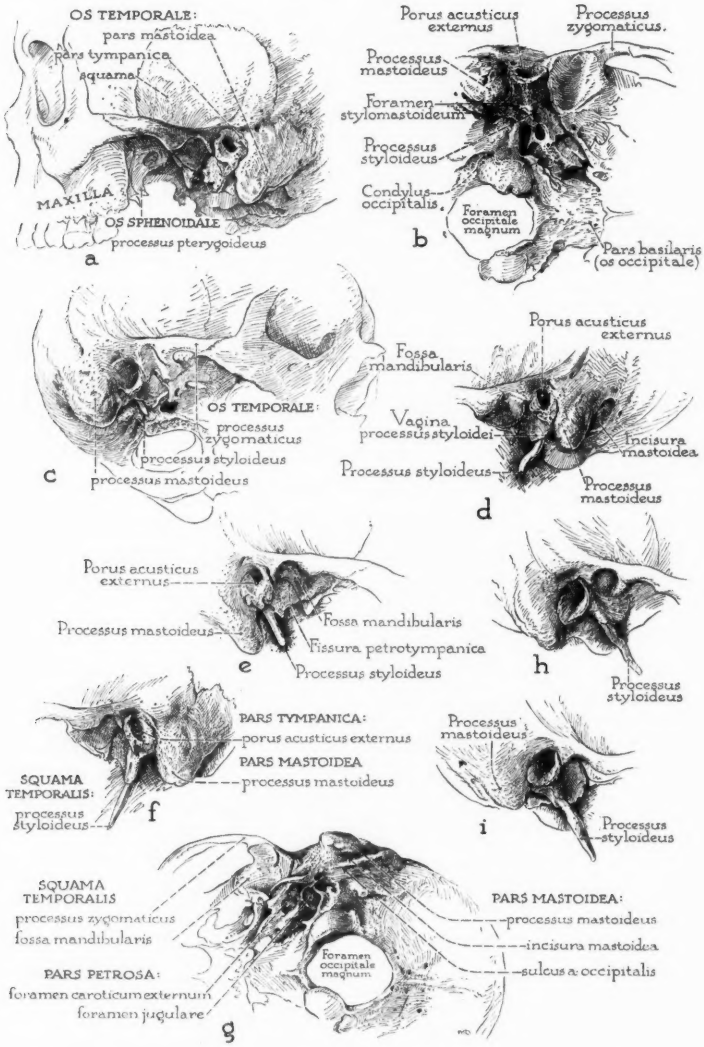

FIG. 12. Skeletal variations in the styloid region of the temporal bone, continued; lateral, inferior, and inferolateral views. Adult skulls. a, A specimen in which a spur, prolonged from the vagina processus styloidei, simulated a true styloid process (as also in 11a). b, An example of true process, but small in size (1 cm. in length). c and d, Processes of medium length (2 cm. and 2.5 cm., respectively). e, A styloid process of greater than average length. f and g, An example of an elongate process (two views of the same skull). h and i, Specimens in which the process, 3.6 centimeters in length, approached the maximum length of 4.2 centimeters for the series of specimens studied.

trunk. Next, in his procedure, the lower pole of the superficial lobe is elevated, and blunt dissection employed. In the evolution of the surgical-anatomic approach to the gland, Adson and Ott advocated a vertical incision in front of the ear which began at the zygoma and was placed in the inframandibular region. The cervical branch is followed upward, the whole gland is exposed, and the surgeon is free to dissect above and then below, according to his desires.

Janes states that the anatomic arrangement between the facial nerve and parotid gland is such that a dissection of the facial nerve, preliminary to excision of the tumor is not only possible but, with some experience, can be done with ease. Janes developed a surgical-anatomic technique for dissection in 1934, and advocated isolation of the main trunk first, in order that there would be less likelihood of injury to the smaller branches. This is accomplished by exposing the sternocleidomastoid muscle and resecting a portion of its insertion, a maneuver which permits exposure of the posterior belly of the digastric and then the trunk of the nerve exposed. Next, the external carotid artery is ligated and the dissection of the facial nerve carried forward to the periphery of the gland.

Another method is that advocated by State, who has had extensive experience with this surgical problem, and whose surgical thinking has been influenced by the work of Bailey, McWhorter, Grégoire, and McCormack and associates. The vertical component of a surgical incision is extended from the zygomatic process to a finger's breadth above the angle of the mandible; a horizontal component under the angle of the mandible then permits raising of the skin flap. The dissection is begun anteriorly, then carried forward until the anterior border of the gland and the parotid duct are seen. The parotid duct is ligated; next, using the small filaments of the facial nerve as guides, the dissection of the nerve is begun by gently retracting the anterior lobe. The cleavage plane between the superficial and deep lobes is thus entered, and the loose areolar tissue is carefully dissected. To aid in this maneuver, gentle retraction is placed on the proximal stump of the parotid duct. The procedure is then carried from anterior to posterior until the isthmus is reached. The main divisions of the facial trunk are identified; the posterior portion of the superficial lobe is located, and by transection of the isthmus, the superficial lobe is removed. The external carotid artery and posterior facial vein are secured and the deep lobe is removed.

Nelson and Deeb prefer to begin the dissection anteriorly, separating the superficial fascia in line with the filaments of the nerve. As soon as a branch of the nerve is found, the overlying fascia is divided and the anterior part of the superficial lobe is elevated. If the tumor is deeply placed, behind the mandible, the mandibular branch of the facial nerve is secured and the main trunk is then isolated. In freeing the nerve filaments, it may be found that glandular tissue had enveloped them, but by blunt separation, with a forceps introduced along the nerve, the fibers can be freed.

In the anterior approach, after the superficial lobe is separated from the nerves, the two main divisions of the facial nerve are found to pass in a groove on either side of the short isthmus. By gently retracting these branches, after they have been freed from the isthmus, the deeper portion of the gland is delivered. When the deep lobe is large and the tumor does not extend into the gland, the isthmus is divided so as to facilitate delivery of the deep lobe.

Clarke has written that in his surgical experience the facial nerve is more easily identified and located because of the bilobed nature of the parotid gland. He further has felt that the various peripheral patterns of the facial nerve in its course through the gland have been of practical aid in its preservation; this general theme has been expressed by Hamilton Bailey.

Recently Patey has described conservative parotidectomy on a limited scale, for chronic "sialectatic" parotitis. Treatment for this pathologic state has formerly been unre-

warding and difficult, but the evolution of this surgical procedure has provided a means for further study of the disease process and a therapeutic weapon.

Not until recently could the late results of facial nerve neurolysis and grafting be dependably evaluated. Martin (29) has reported upon such cases, and his results extend the applicability of an encompassing knowledge of the parotid area and the peripheral course of the facial nerve.

CONCLUSIONS

Anatomic and surgical literature, as well as present-day textbooks of gross anatomy, all seem to be wanting in their accounts of the parotid gland, its vascular relations, its intimate association with the facial nerve and adjacent bony landmarks. To date, there has been no adequate description of the parotid duct-system, and the conventional textbook usually portrays the gland as being surrounded by a fascial sheath which is in continuity with the deep cervical fascia. The familiar cross-section diagram pictures the parotid gland as a single-lobed structure, whose posteromedial portion extends into the retropharyngeal space; and the main facial nerve trunk and its peripheral branches are seen deeply buried within the parotid salivary tissue.

It remained for Grégoire, verifying a statement by Luschka, to record the parotid gland as a bilobed structure, the interspace allowing for passage of the facial nerve. Later McWhorter improved upon earlier description; the surgical writings of a considerable number of authors, and particularly that of Hamilton Bailey, have supported the concept of a bilobed gland. In recent years this fact, long forgotten, has been generally accepted. However, some writers have contended that the matter is of academic interest alone, and that the surgeon attempts to preserve the facial nerve by avoiding it, and not following the laminar plane between the lobes.

The observations presented herein are in general agreement with those reported in an earlier account by McCormack, Cauldwell, and Anson. Further dissection experience, in the same laboratory, with 350 facial halves showed that the facial nerve and its peripheral rami were distributed between the deep and superficial lobes of the gland, and that in this location the main facial trunk divided into temporofacial and cervicofacial portions. The numerous relationships between the branches of these two main divisions afforded an opportunity to catalog six distinct nerve patterns; between the more simple arrangements and the most complicated were several types of moderate complexity, based on the number and character of anastomoses between the branches of the two main divisions.

Most convenient sources omit a description of the extraglandular duct system; careful laboratory study has shown that the ductules contributing to the main parotid duct arose from the superficial lobe or from both the superficial and deep leaves in 75 per cent of the specimens examined. Similarly, related vascular structures are stylized, and although far from regular, the arterial patterns in this area are far less variable than the system of venous tributaries. The transverse facial artery and external carotid artery have a relatively fixed relationship to the parotid gland, as is true of the anterior and posterior facial veins.

The styloid process, as classically pictured, is a well developed skeletal landmark of the normal skull. However, in the large series of skulls examined by the present authors, it was absent in over one-third of the cases, shielded completely or nonpalpable in many others. Consequently, its usefulness as a surgical landmark is quite limited.

Most conventional references credit the parotid gland with a definite fascial sheath or investment, which is described as being continuous with the deep cervical fascia. The surgeon is prepared to encounter a structure which most sources describe as being a firm capsule of considerable extent and strength. Actually, the outer lamina is the layer of fascia which contains platysma muscle. In

the dissection laboratory this layer is not one of great prominence; rather, it is loosely applied, being connected to the gland by numerous septa sent inward among its lobules. The inner lamina is merely the investing fascia of the masseter muscle. When care is taken, it is possible to demonstrate fusion between these two laminae along the periphery of the gland.

Various authors of surgical articles have described techniques by which the facial nerve can be partially or wholly preserved during parotidectomy in cases of glandular tumor. Whether the dissection be commenced anteriorly or posteriorly, or whether the cervical branch of the facial nerve or posterior facial vein be used as a convenient landmark to develop the natural cleavage plane, successful excision should be possible. Regardless of the order in which the several surgical steps are taken, it seems that anatomic knowledge of the whole region would have basic value in providing information on the range of normal variation in neurovascular structure, skeletal anatomy, interrelationships of duct system and nerve rami, range in variation of position, and dimensions of the gland itself.

With increasing incidence of facial and other cranial nerve anastomosis for facial palsies, and the well documented fact that mixed tumors of the parotid gland tend to recur because of limited surgical excision, new importance is attached to any account which deals critically with the anatomy of this long neglected area.

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THE ETIOLOGY AND TECHNIQUE OF SURGICAL MANAGEMENT OF PANCREATIC FISTULA

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A PANCREATIC FISTULA, with its loss of fluid and electrolytes and its autodigestion of skin surfaces, is one of the most serious complications of surgery. Formerly, it usually followed marsupialization of pancreatic cysts, but it is now more often due to damage to the pancreas during gastric resection, biliary surgery, or splenectomy. Less commonly, fistula may result from the necrosis which accompanies acute pancreatitis or from injuries to the upper abdomen.

EMBRYOLOGY OF PANCREATIC DUCTS

The variations in anatomy of the pancreatic duct system arise from its peculiar embryologic development. The pancreas develops from two buds arising from the duodenum (Fig. 1A), a dorsal bud which arises separately and a ventral bud which usually arises with the bile ducts. The ventral bud rotates dorsally and to the left (Fig. 1B) and when the embryo is about 12 millimeters long, it fuses with the dorsal bud (Fig. 1C). The ducts of the dorsal and ventral buds acquire a connection with each other (Fig. 1D). The ventral bud forms the lower part of the head of the pancreas and the dorsal bud forms the remainder. The main pancreatic duct (of Wirsung) is, therefore, formed distally by the duct of the dorsal bud and proximally by the duct of the ventral bud. It usually opens with the common bile duct onto the ampulla of Vater. The proximal part of the original dorsal duct persists as the accessory duct (Fig. 1E).

ANATOMIC VARIATIONS OF PANCREATIC DUCTS

Growth or recession of various portions results in one of the three final arrangements shown in Figure 2 (Grant). In 61 per cent of cases the accessory duct loses all significant duodenal connection, and the main duct and accessory duct open together with the common bile duct (Fig. 2A). In 30 per cent of cases the accessory duct retains a separate opening and is large enough to relieve or substitute for the main duct (Fig. 2B). In 9 per cent of cases the primitive dorsal duct persists, usually quite unconnected with the primitive ventral duct (Fig. 2C).

A further variable feature is the mode of entry of the bile and main pancreatic ducts into the duodenum. In 95 per cent of cases they share a common opening (Fig. 2A and B), but in 5 per cent the common bile duct opens separately from the main pancreatic duct (not illustrated).

INJURIES TO PANCREATIC DUCTS

Cedermark quotes several extensive investigations into the anatomy of the pancreatic ducts. These showed that when the pancreas is hammer-shaped and has a large head, the accessory duct is more likely to be large and accessible to injury than when the pancreas is tongue-shaped and the head small.

Millbourn injected 200 specimens with radiopaque material and concluded that in 50 per cent of gastrectomies for duodenal ulcer, the duct of Santorini is in danger of injury during dissection of the duodenum from the pancreas. Finsterer recommended that in difficult duodenal ulcers the base of the ulcer be left in situ. Cattell and Warren believe that if an injured accessory duct is small, as it usually is, the leakage will be

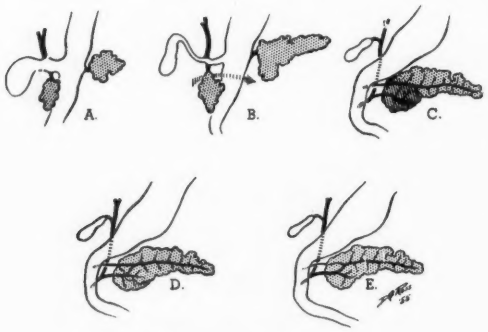

FIG. 1. Embryology of the pancreas.

slight and temporary. If the injured accessory duct is large and not ligated, the leakage will be serious or fatal. Nonabsorbable suture material is best for ligation. Injuries to the main duct are less common but more serious. The main pancreatic duct lies more superficially in the body and tail of the pancreas than in the head and, therefore, may be injured during the removal of adherent gastric ulcers. Division of the main duct without ligation may produce widespread necrosis or persistent fistula. Division with ligation may produce delayed fistula or pancreatic insufficiency.

PHYSIOLOGY OF PANCREATIC SECRETIONS

The physiology of pancreatic secretion has been studied by duodenal aspiration in normal patients and also in patients with fistulas. There is a continuous flow of juice, variously estimated at from 500 to 2,400 cubic centimeters per day. There is a considerable increase in the volume of pancreatic juice for about 3 hours after eating. Secretion is stimulated by two means:

Nervous. Vagus stimulation causes an outpouring of a small amount of juice, rich in enzymes. In the case to be described, banthine had no effect on the daily volume of juice.

Chemical. Gastric hydrochloric acid, bile salts, or food, on reaching the duodenal mucosa, cause it to release two hormones which are carried by the blood to the pancreas, viz., (a) secretin, which stimulates the secretion of a large volume of juice low in enzymes, and (b) pancreozymin, which produces a small amount of juice rich in enzymes. As the gastric hydrochloric acid is neutralized by alkaline pancreatic juice, the chemical stimulus is decreased. If a fistula exists this automatic control is lacking, hence the volume of pancreatic juice secreted is probably greater than normal. Aldis points out that this observation accounts for the higher estimates of pancreatic secretion (2,400 c.c. per day) which were obtained in patients with fistulas.

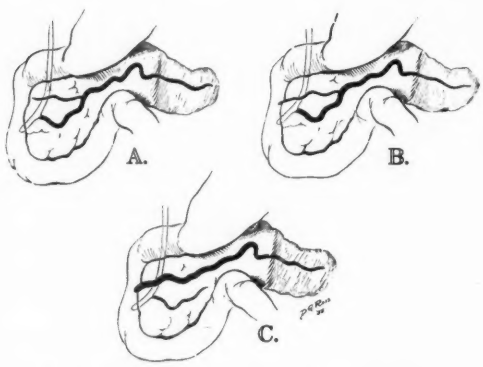

Fig. 2. Variations in anatomy of pancreatic ducts.

Pancreatic juice contains three enzymes: amylase, which converts carbohydrates to maltose; lipase, which, with the aid of bile, splits neutral fats to diglycerides, monoglycerides, fatty acids, and glycerol; trypsin, which digests proteins to polypeptides or further. Trypsin is secreted in an inactive form, trypsinogen. Trypsinogen is converted to trypsin by enterokinase in intestinal secretions. Other substances such as bacteria and bile salts may also activate trypsinogen, thus accounting for the digestion of the skin which occurs around a fistula. Trypsin acts best in an alkaline medium. Tannic acid was therefore used as a skin protective by Lahey. We found tan-gel effective.

A knowledge of the electrolyte composition of pancreatic juice is important in dealing with a fistula. The concentrations of sodium, potassium, and calcium in the

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 3. Pancreatic duct as shown by injection of lipiodol into fistula.
FIG. 4. Photograph taken May 8, 1952. Patient weighed 85 pounds.
FIG. 5. Photograph taken January 19, 1956. Patient weighed 171 pounds.

pancreatic juice are the same as in the blood plasma. Chloride is somewhat lower and bicarbonate somewhat higher than their respective plasma levels. The features of prolonged loss of pancreatic fluid are chiefly those of sodium deficiency—lethargy, sense of exhaustion, anorexia, nausea, dehydration, reduced blood volume, and loss of extracellular fluid.

TREATMENT OF PANCREATIC FISTULAS

Many methods of treatment have been tried in the past and these may be classified as follows:

1. No active treatment in the hope of spontaneous closure. The natural history of pancreatic fistula is so variable that one cannot predict the outcome in any individual case and this must be borne in mind when assessing the value of any treatment. Of 88 cases reviewed by Lahey, 62 fistulas closed spontaneously within 1 year. The remainder drained for more than 1 year, and 1 drained 500 cubic centimeters daily for 21 months, then closed spontaneously.

2. Drug therapy, in an attempt to reduce the volume of fistula flow to the point at which the fistula may close spontaneously. Many substances have been investigated and may be grouped as follows: (a) those causing no significant drop in the volume of secretion, e.g., glucose, sodium bicarbonate, banthine, and smoking; (b) those causing a definite but temporary drop in volume of secretion, e.g., ephedrine, atropine, morphine, adrenaline, physostigmine, and pilocarpine. The latter two drugs probably act by stimulating adrenaline secretion. Ephedrine has the greatest effect, but no drug has given consistent results.

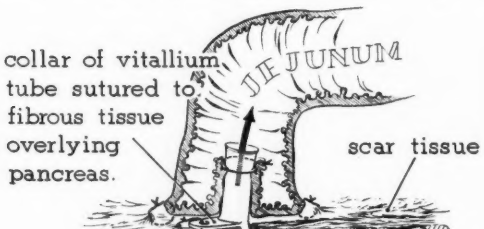

FIG. 6. Method of anastomosis of jejunum to base of fistula.

3. Dietary methods. (a) A low carbohydrate diet (Wohlgemuth's diet) was the standard treatment for years, but it is now considered to have little if any effect. (b) Although some believed a high carbohydrate diet was superior to Wohlgemuth's diet, the natural variation in outcome probably accounts for the successes occasionally attributed to it. (c) Dehydration therapy has also been attempted. The volume of pancreatic juice, like saliva, is influenced by the state of body hydration. Thomas and Ross described an instance in which a fistula, draining 600 cubic centimeters per day, closed in 10 days by withholding all oral feedings and giving only amigen and glucose in water intravenously, to a total of 2,000 cubic centimeters per day. This treatment was unsuccessful in our case, although it did temporarily reduce the volume of flow.

4. X-ray and radium therapy have been investigated by Fisher, Ivy, Leven, Miller, and Orndoff, but there are not a sufficient number of case reports to determine whether they have any practical value. Culler reported 2 cases and Miller reported 1 case of cure of a pancreatic fistula by irradiation.

5. Few surgeons have had experience with many cases of pancreatic fistula, and operative reports are scarce and often brief. Some operations for fistula have been described briefly in articles dealing with other topics and so are not readily found in searching the literature. (a) Miller and Wiper reported a case in which the tract was simply dissected down to the pancreas and ligated. The fistula recurred and finally closed spontaneously. Others have had similar recurrences after this type of operation. (b) Lahey and Lium in 1937 reported a pancreatic fistula which followed a blow to the abdomen, lacerating the pancreas. It had drained up to 650 cubic centimeters daily for 5 months. They treated it successfully by a two stage procedure. They first dilated the fistulous tract up to a French No. 22 sound. Following this dilatation, the tract was mobilized and the end of the fistula was introduced into a loop of jejunum with a catheter in situ to maintain patency. This technique has been used successfully by others. However, Cattell and Warren reported in 1953 that the operation may fail because of stenosis of the fistulous tract. Our experience to be described confirmed this observation. (c) Doubilet and Mulholland cured a 3 year pancreatic fistula by division of the sphincter of Oddi, excision of the fistulous tract, and anastomosis of the base of the fistula to the stomach. The severity of the fistula or the length of follow-up period is not stated. They attributed the result chiefly to the sphincterotomy which allowed easier drainage. They also used sphincterotomy in the treatment of pancreatic cysts. (d) Peterson and Cole, in 1948, reported the successful treatment of a pancreatic fistula which had followed marsupialization of a pancreatic cyst by excision of the fistulous tract and anastomosis of the stump of the fistula to a loop of jejunum with a lateral enteroanastomosis below. (e) Cattell and Warren, in 1953, recommended that fistulas caused by division of the duct of Wirsung in the head of the pancreas be treated by suturing the divided end of the duct to the duodenum or jejunum with mucosa-to-mucosa approximation. If the fistula has resulted from drainage of a

cyst in the head of the pancreas, they advised excision of the tract and anastomosis to the jejunum. If the fistula is from the body or tail of the pancreas, they recommended excision of the distal part of the pancreas, including the segment from which the fistula arises.

In the case report to follow, a Lahey-Lium operation failed either because of stenosis of the fistulous tract or because of retraction of the fistula from the bowel. At a second operation the fistula was excised to its base and the stump of the fistula anastomosed to a single arm of jejunum by using the Roux Y principle. The case is described in some detail because of the severity of the fistula, its long duration, and the complications which required special measures.

CASE REPORT

A 38 year old farmer was admitted to the public ward of the Winnipeg General Hospital on December 8, 1954. In 1947 he had had an operation for perforated duodenal ulcer. Surgery was recommended for intractable duodenal ulcer. On December 13, 1950 the surgeon found a large inflammatory mass around the pylorus and duodenum. He decided that one stage resection was hazardous and excised the distal portion of the stomach, leaving the pylorus and the inflammatory mass in situ. A posterior Polya anastomosis was done. The patient made an uneventful recovery and was discharged December 26, 1950.

On readmission on February 1, 1951 for second stage operation, he felt well and had gained 12 pounds. At operation February 5, 1951, the inflammatory mass had disappeared. According to the record 2 centimeters of stomach and 7 centimeters of duodenum were removed. The duodenum showed chronic inflammation, but no ulcer. The surgeon found it necessary to leave a 2 centimeter patch of gastric mucosa adherent to the posterior abdominal walls. No drain was used. In retrospect, one wonders whether the original ulcer was prepyloric, duodenal, or both.

On February 16, 1951 a clear, watery wound discharge appeared, which contained amylase but did not digest the skin, suggesting that it came from the remnant of gastric mucosa rather than the pancreas. The patient developed a temporary bowel obstruction which corrected itself.

On March 14, 1951, the draining sinus was traced to the patch of gastric mucosa which contained a penetrating ulcer, overlying the pancreas. The gastric mucosal remnant and a 5 centimeter cuff of stomach

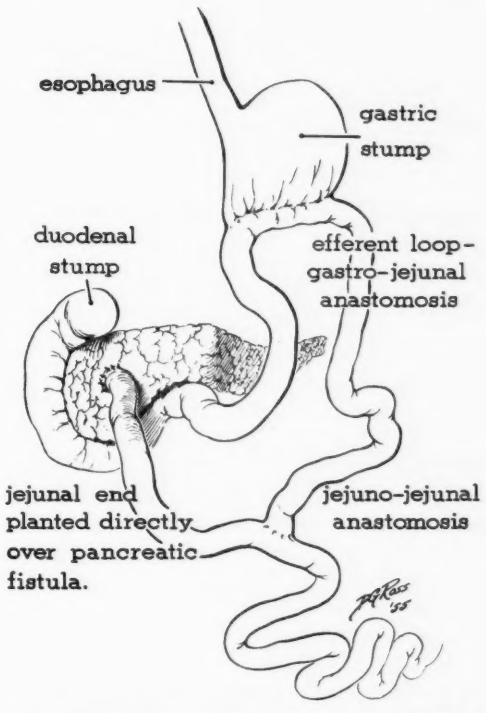

FIG. 7. Final arrangement after internal drainage of pancreatic fistula resulting from subtotal gastrectomy.

were removed. Postoperatively the discharge increased to 1,200 cubic centimeters per day and began to digest the skin. Lipiodol injection of the sinus outlined the pancreatic duct and smaller radicles and some of the dye passed into the duodenum (Fig. 3). The stools were pale, bulky, fatty, and foul-smelling.

He was then treated for 10 days by the Thomas and Ross method of witholding all oral feedings and giving only 2,000 cubic centimeters of glucose with amigen daily intravenously. Dr. J. A. Hildes of the Department of Medical Research directed this treatment and reported the results. The fistula drainage decreased from 1,200 to 300 cubic centimeters per day, but with feeding returned to 1,200 cubic centimeters. During this 10 day period his blood sodium, potassium, and chlorides did not change appreciably because the kidney conserved these ions. The blood volume remained constant at 5,700 cubic centimeters. He lost 11 pounds but felt fairly well. Banthine did not affect the volume of pancreatic juice.

On May 25, 1951 we performed the Lahey-Lium operation. The distal 2½ inches of the fistulous tract were mobilized and planted into a loop of upper jejunum leaving a rubber catheter in situ in the lumen of the fistula. An anteroanastomosis was done

below the apex of the loop. In the first 10 postoperative days he gained 17 pounds and felt well. There was no drainage and the stools became normal. However, on June 12, the catheter was passed per rectum, and a few hours later he developed abdominal cramps and nausea. The fistula had not yet recurred. The fecal fat constituted 30 to 50 per cent of the weight of the dry stool. He was discharged feeling well on June 28, 1951.

Five days later he was readmitted with signs of massive right pleural effusion. Nine hundred and sixty cubic centimeters of pancreatic fluid were aspirated from the right pleural cavity and continuous closed intercostal drainage was begun. On July 26 a right anterior subphrenic abscess was drained, yielding 200 cubic centimeters of pus containing Bacillus coli and Bacillus proteus. This was followed by a discharge of 1,500 cubic centimeters per day of clear pancreatic fluid. By August his weight was 80 pounds, and he developed another small bowel obstruction, treated by division of an adhesion. The pancreatic juice was collected by continuous suction and given with the feeding mixture, maintaining normal electrolyte balance. He developed bilateral phlebitis treated by dicumarol.

On September 29, 1951 he was found to have a left pleural empyema and 250 cubic centimeters of pus were aspirated, culturing Bacillus coli and streptococci. Because he was so ill the empyema was treated by continuous closed drainage and irrigation with Dakin's solution.

In October 1951, he weighed 121 pounds. The fistula had stopped draining for 3 weeks only to recur. He was too weak to stand and was still tube fed. By December 1951, the roentgenograms of the chest were clear. The pancreatic fistula stopped spontaneously for another 3 week period but then drained continuously 400 to 900 cubic centimeters per day. In March 1952, a roentgenogram of the chest showed a small abscess in the lower lobe of the left lung, which on bronchoscopic aspiration cultured Bacillus proteus and streptococci. Under treatment with antibiotics and postural drainage, this cleared by May 1952.

During this 14 month period with almost continuous drainage of 400 to 1,500 cubic centimeters of pancreatic fluid per day his general condition was maintained through the liberal use of tube feeding (with fistula juice added), blood transfusions, intravenous therapy, sodium and potassium salts, antibiotics, vitamins, pancreatic extract, testosterone, fat emulsifiers, sodium alkaline phosphate to aid fat absorption, and other aids. Various substances, including aluminum paste and powder and plastic cements, were used to protect the skin from digestion. The most efficient method was continuous suction by an electric pump on a sump catheter inserted in the sinus tract. This procedure also enabled collection of the juice for feeding.

By May 8, 1952, we believed that there was almost no hope of spontaneous closure and that although his general condition was poor (Fig. 4), the only chance for survival lay in another attempt at surgical cure.

A simple operation was conceived and in practice proved quite feasible. The abdomen was opened by an inverted T incision in the epigastrium. With a ureteral catheter threaded into the fistulous tract as a guide, the tract was carefully dissected down to its origin on the pancreas. The tract was divided where it emerged from the scar tissue overlying the pancreas and the superficial portion of the tract was excised. The remaining (deep) portion of the tract was probed and dilated with a hemostat up to approximately 0.8 centimeter in diameter. A vitallium tube 3 centimeters long and 0.6 centimeter in diameter was inserted into the mouth of the fistula and fixed by a silk suture through its collar to the adjacent scar tissue. The loop of jejunum into which the fistula had been transplanted at the previous operation had become completely detached from the fistula and this segment of jejunum was resected including the previous enteroanastomosis. The ends were anastomosed because the area was too close to the duodenojejunal junction to use in the next step. A more distal loop of jejunum was divided and the distal cut end brought up in a retrocolic position to the site of the fistula. The open end of jejunum was then sutured to the posterior abdominal wall directly over the mouth of the fistula, with the vitallium tube maintaining patency (Fig. 6). This was accomplished by a purse-string silk suture inverting the end of the jejunum over the vitallium tube. The periphery of the inverted bowel was then sutured to the scar tissue surrounding the fistulous tract with interrupted silk. An end-to-side jejunojejunal anastomosis (Roux Y) below this completed the operation. The final arrangement is shown in Figure 7.

In the first 2 postoperative months he gained 20 pounds, had an excellent appetite, and, although still weak, began to get up. The glucose tolerance test was normal. The stools were still pale and foul-smelling and had a fat content of 40 per cent by dry weight. He was discharged on July 23, 1952.

On examination 3½ years postoperatively, there has been no recurrence of the fistula. He weighs 171 pounds (Fig. 5) and works as a farmer. Although he complains of eye fatigue, backache, and occasional abdominal cramps, these are not severe enough to keep him from working. He has 2 soft stools per day, a random sample containing 30 per cent total fat, dry weight. He follows no special diet and takes no medicines. There is no glycosuria.

SUMMARY

1. The embryology and anatomy of the pancreatic ducts have been reviewed.

2. The physiology of pancreatic secretions has been outlined.

3. The etiology, natural history, and treatment of pancreatic fistulas have been described.

4. A case history is presented in which a pancreatic fistula drained 400 to 1,500 cubic centimeters of fluid daily for 14 months. During this time the patient became emaciated, suffering in turn from rupture of the pancreatic fistula into the right pleural cavity, subphrenic abscess, repeated intestinal obstruction, left lung abscess, left empyema, and bilateral phlebitis. The fistula recurred after a Lahey-Lium operation.

5. The fistula was cured by an operation which is described in detail. Three and one-half year follow-up examination shows no recurrence.

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IN VITRO AND CLINICAL EFFECTS OF URETHANE PLUS TRIETHYLENE MELAMINE ON HUMAN BREAST CANCER

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SINCE A CONSIDERABLE NUMBER of breast cancer patients ultimately die of their disease the problem of palliative therapy is of decided clinical importance. Unfortunately, however, the palliative chemotherapeutic agents which are of such striking value in the lymphomas and in allied diseases are only sporadically effective in human breast carcinoma. Furthermore, in view of their marrow toxicity one hesitates to use them routinely in the hope of benefiting an occasional patient. It would, therefore, be desirable to find some combination of antitumor agents which would be effective in a greater percentage of cases without increased toxicity and some method of selecting patients having a greater than average likelihood of being helped by such treatment.

In 1953, we reported upon the in vitro effects of ethyl carbamate (urethane) and triethylene melamine (TEM)[1] both singly and in combination, on the dehydrogenase activity of human cancer tissue slices (3). It was found that the combination of urethane plus TEM inhibited such in vitro tumor slice metabolism more frequently and to a greater extent than either agent alone. These studies were extended, and in 1954 we reported on a series of cases wherein the effects of aminopterin (4-aminopteroyl glutamic acid) alone and in combination with urethane and TEM were also studied (4).

Our findings suggested that the use of the combination of urethane plus TEM or methyl-bis(β-chloroethyl)-amine (HN2) might be of greater clinical efficacy than either agent alone. Skipper found evidence of such a chemotherapeutic synergism when this combination was tested against certain experimental tumors. Our initial clinical studies on the use of urethane plus TEM in diverse human cancer cases also gave evidence of such effects (4).

The present article is a presentation of measurements of the in vitro metabolic activity of tissue slices from 94 cases of breast carcinoma as well as a report of the clinical effects of urethane plus TEM or HN2 on 21 cases of breast carcinoma. In 7 of these 21 cases both in vitro and clinical observations were made. The data obtained indicate the existence of a synergistic action between urethane and TEM on the in vitro dehydrogenase activity of human breast carcinoma as well as a chemotherapeutic synergism. In addition, the in vitro measurements appear to be correlated with the clinical effects in the individual cases, thus allowing for case selection.

MATERIAL AND METHODS

Measurements were made of the in vitro endogenous dehydrogenase activity of tumor tissue slices from 94 human breast carcinomas. In most instances such tissues were obtained from the primary tumors removed at the time of the original definitive diagnosis. In some cases the tissues were from skin metastases in cases of disseminated disease. Determinations were also made of the in vitro effect of urethane, TEM, and urethane plus TEM in 94, 78, and 77 cases respectively. The technique of these procedures has been described in previous reports (3, 4).

The clinical studies were made on patients with widely disseminated disease. In approximately half of these cases x-ray therapy

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Aided by grants from the Leukemia Research Foundation and the Schering Corporation.

[1]Triethylene melamine will be referred to throughout the article as TEM, ethyl carbamate as urethane, and methyl-bis(β-chlorethyl)-amine as HN2.

had proved ineffective as a palliative agent. In general the chemotherapy was administered over a period of 8 days during which time 2 to 3 grams of urethane were given daily either orally or in an infusion of 500 milliliters of 5 per cent glucose in water. The TEM was given on alternate days; 5 milligrams on the second day of the course and then 2.5 milligrams every other day for 3 doses.

The response to therapy was evaluated according to subjective and objective effects and graded as good, fair, and poor, viz., marked relief of pain without any evidence of regression of tumor masses or changes in neurologic findings would be considered as a good subjective response but a poor objective effect.

In 3 cases it was possible to obtain pretreatment and posttreatment biopsies of the tumor tissue thus allowing an evaluation of the structural changes induced by the urethane plus TEM therapy.

RESULTS

In vitro measurements. In Table I we have listed the effects of urethane and TEM, singly and in combination on the in vitro dehydrogenase activity of human breast cancer tissue slices. It will be seen that the incidence of the various degrees of inhibition by urethane and by TEM was every similar. It should be mentioned, however, that when the findings in the individual cases were evaluated it was found that while the inhibition by urethane was essentially similar to that of TEM in about 40 per cent of the cases, in 32 per cent of the cases the TEM inhibition was at least 15 per cent greater than that produced by urethane. The converse was true in 28 per cent of the cases.

The inhibitory effect of urethane plus TEM was distinctly greater than that produced by either agent alone. Forty-three per cent of the cases were inhibited a minimum of 30 per cent by this combination. In contrast this degree of inhibition was found in only 32 per cent of the cases in the urethane series and in 28 per cent in the TEM series. In the individual cases, the inhibition by the combination of urethane plus TEM was at least 15 per cent greater than that produced by urethane or TEM alone, in 40 and 46 per cent of the cases respectively. In only 11 per cent of the cases was the degree of inhibition by the combination less than that produced by either agent alone.

TABLE I.—PER CENT INCIDENCE OF DEGREE OF INHIBITION OF IN VITRO DEHYDROGENASE ACTIVITY BY URETHANE AND TEM, SINGLY AND IN COMBINATION

Agent	*No. of cases*	*Degree of inhibition, per cent*			
		<15	*15–29*	*30–44*	*>44*
Urethane	94	44	23	22	10
TEM	78	43	24	20	8
Urethane+TEM	77	26	31	26	17

Clinical effects. In Table II we have listed the chemotherapeutic effects of urethane plus TEM. When such data were available we have also indicated the in vitro effects observed in the individual cases. Of the 14 patients treated without in vitro measurements the objective response was good in 4 cases, fair in 5 cases, and poor in 5 cases. Of the 7 patients with in vitro measurements the clinical effects were good in 5 cases and poor in 2 cases. In each of the 5 patients with good clinical response the in vitro inhibition by urethane plus TEM was greater than 40 per cent. In contrast the urethane plus TEM inhibition values were 14 and 24 per cent in the tissues from the 2 patients who responded poorly.

In 3 cases, in vitro measurements, clinical study, and pretreatment and posttreatment tissue examinations were possible. The illustrative features of these cases are as follows:

I. F., a 37 year old white female, underwent a left radical mastectomy for carcinoma in April 1947. Four months previously she had delivered a full term child. She was asymptomatic till January 1951 when she developed a cough, chest pain, and nodular recurrences in the skin. A good therapeutic response was obtained by local x-ray therapy. Recurrent skin nodules and a gasserian ganglion syndrome appeared within a few months and were controlled by further x-ray therapy. However, the lesions soon reappeared and by April 1952 she was hemiplegic on the left side, hemiparetic on the right side, and semicomatose. In addition, bladder and rectal incontinence was present as well as numerous tumor nodules in the skin of the

TABLE II.—CLINICAL AND IN VITRO EFFECTS OF URETHANE PLUS TEM ON HUMAN BREAST CANCER TISSUE

Case	*In vitro, per cent*	*Subj.*	*Obj.*	*Comment*
I.F.	49	G	G	See text
V.D.	45	G	G	See text
M.M.	41	G	G	See text
E.G.	50	G	G	Regression of skin and hepatic metastases
E.S.	41	G	G	Regression of skin nodules and plural effusion
S.R.	24	P	P	Cancer en cuirasse—no effect
R.K.	14	P	P	Pulmonary involvement—no effect
B.K.		G	G	Spinal metastases, unable to walk—relief of pain and ambulation
I.S.		G	G	Regression of massive hepatomegaly
R.W.		F	F	Diminution in pain and increased ability to walk
E.K.		F	F	Diminution in pain and increased ability to walk on 3 occasions
B.S.		G	G	Diminution in pleural effusion and dyspnea
B.B.		F	F	Decrease in pain and increased physical activity
J.G.		P	P	Hepatic and pulmonary metastases—no effect
V.M.		P	P	Skin and pulmonary lesions—no effect
A.S.		G	P	Some diminution in bony pain. No apparent effect on progression of disease. Pulmonary metastases
F.D.		G	F	Marked diminution in pain, increased ability to ambulate, moderate decrease in dyspnea on 2 occasions
F.C.		F	F	Transient relief of pain and regression of neurologic finding
T.T.		P	P	Cerebral and bone involvement—no effect
C.P.		P	P	Inoperable primary lesion and skull metastases—no effect
A.K.		G	G	Relief of pain, increased ambulation, decreased dyspnea

chest and abdomen. On April 4, 1952 a skin nodule was removed for in vitro metabolic studies (Fig. 1). A urethane plus TEM inhibition of 49 per cent was found. The next day she was started on a course of urethane and TEM.

Her clinical status deteriorated for a few days and then began to improve progressively. By May 8, 1952 she had received a total of 49 grams of urethane and 5 milligrams of TEM. Her sensorium was clearer, she was able to sit in a chair, and the skin nodules were definitely smaller in size. It was decided to continue a maintenance dose of urethane, and by June 30, 1952 she was discharged from the hospital in an ambulatory condition, with her mental status good and with full rectal and bladder control. During her hospital stay she had received a total of 127 grams of urethane and 5 milligrams of TEM. The white blood count was 5,900 per cubic millimeter and the hemoglobin was 14.0 grams at that time.

She was active and essentially asymtomatic until early in April 1953 at which time she noted lightheadedness and the appearance of minute nodules in the skin of the chest. She was observed for a period of 3 weeks during which time the complaints were accentuated and the skin nodules increased in size and number. On April 21, 1953 she was started on urethane plus TEM. She received 24 grams of urethane and 10 milligrams of TEM over an 8 day period. On April 28 an area of herpes zoster developed on the chest wall at the level of fifth and sixth thoracic vertebrae on the right side. Coincident with the completion of the chemotherapy there was some regression of the skin nodules and improvement in well being. However, on May 1, 1953 she suddenly became aphornic, underwent clonic convulsions, and became comatose. She was hospitalized and treated symptomatically.

The next day she appeared to be able to understand, and by May 6 she was able to move and speak and was free of convulsions. However, her white blood cell count fell from an admission value of 13,000 per cubic millimeter to 3,700 per cubic millimeter by May 4. On May 7 she developed a herpetic eruption over the trunk, extremities, and face which became focally hemorrhagic. Blood cultures were negative as were cultures of the skin lesions. The temperature which had been only moderately elevated, began to spike to 104 degrees F., the white cell count fell to 600 per cubic millimeter, and the platelets to 60,000. The mucous membranes of the mouth became extensively involved by the herpetic lesions and the patient became increasingly toxic despite supportive therapy and antibiotics. She expired on May 13, 1953.

A complete autopsy was performed the next day. The pertinent findings included carcinomatous involvement of the skin, brain, lungs, bone, adrenals, and liver. The tumor cells showed giant cell formation, nuclear aberrations, and pyknosis which were not seen in the original lesions or the skin biopsy (Fig. 2). The skin showed typical herpetic lesions with intranuclear eosinophilic inclusion bodies. The esophagus showed evidence of gangrenous esophagitis with inclusion bodies in the nuclei of the squamous cells while the gastric mucosa showed numerous shallow ulcers.

This case is an example of an unusually long remission from disseminated breast carcinoma coincident with urethane plus TEM therapy. In addition, the reactivation of the

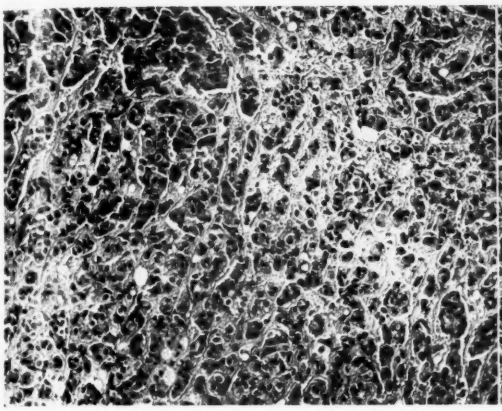

FIG. 1. Patient I. F. Skin metastases from breast carcinoma before chemotherapy. ×55.

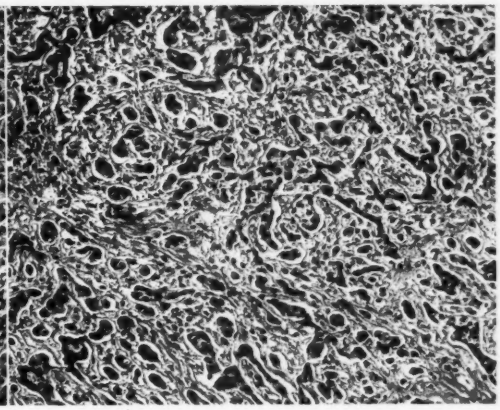

FIG. 2. Lymph node metastases from breast carcinoma. Autopsy findings after urethane plus TEM therapy. ×55

tumor, 1 year after the initial chemotherapy, was also responsive to urethane plus TEM therapy. The posttreatment appearance of the tumor was characterized by aberrations in nuclear structure which provided direct evidence of a tumor cytotoxic effect of the therapy. The immediate cause of death in this case appeared to be related to the systemically disseminated herpes which was complicated by a hemorrhagic tendency. The latter finding was very probably the result of the thrombocytopenic effect of the therapy employed.

V. D., a 44 year old white female, had a left radical mastectomy for carcinoma in April 1954. In vitro metabolic studies were performed at that time and revealed a urethane plus TEM inhibition of 45 per cent. In September 1954 an oophorectomy was performed. In June 1955 she developed pain in the right subcostal region and examination revealed marked hepatomegaly. A needle biopsy disclosed metastatic carcinoma of the breast to the liver (Fig. 3). Testosterone therapy was given with no apparent benefit, and on July 14, 1955 she was started on a course of urethane plus TEM; (urethane, 24 gm., TEM, 12.5 mgm. for an 8 day period). Symptomatic relief was noted about 1 week after completion of this treatment, as well as some decrease in the size of the liver. On August 8, 1955 additional therapy was given in the form of urethane, 20 grams, and TEM, 7.5 milligrams, for a 10 day period. Coincident with this treatment the liver decreased progressively in size and was no longer palpable by the completion of the treatment. A repeat liver biopsy was performed on August 23, 1955. It showed extensive cytonecrosis of the tumor cells (Fig. 4). As of October 4, 1955 the liver has remained nonpalpable, and the patient is much improved clinically.

This case revealed an excellent correlation between the in vitro measurements and the clinical effects of urethane plus TEM. It also illustrates the favorable response that may occur in selected cases of disseminated breast carcinoma treated with urethane plus TEM. The pretreatment and posttreatment biopsies provided direct evidence of the cytonecrotic potency of the therapy employed.

M. M., a 47 year old white female, was admitted to Flower and Fifth Avenue Hospitals on July 29, 1951 for removal of a mass in the left breast of 4 weeks' duration. Frozen section examination revealed carcinoma of the breast, and a radical mastectomy was performed on July 30, 1951. She also received postoperative regional x-ray therapy and radiation castration. In the latter part of 1952 recurrent skin nodules were noted and she received regional x-ray therapy intermittently until January 20, 1954. At that time it was apparent that the x-ray therapy was no longer capable of controlling the lesions. She had also received testosterone therapy without any apparent benefit. In vitro metabolic studies were performed and revealed a 41 per cent inhibition by urethane plus TEM.

During the period, January 29, 1954 to February 8, 1954, she was given 10 milligrams of TEM and 30 grams of urethane. This was followed by marked sloughing of the tumor and subsequent healing. However, by May 1954 she had recurrent skin nodules and back pain and was given additional TEM (12.5 mgm.) and urethane (32 gm.) for an 8 day period. This treatment was again

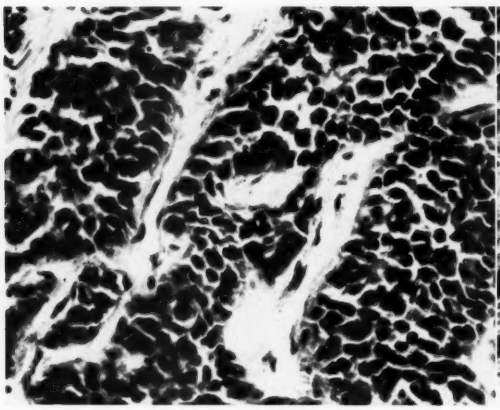

FIG. 3. Patient V. D. Needle biopsy of liver showing metastatic breast carcinoma before administraton of chemotherapy. ×250.

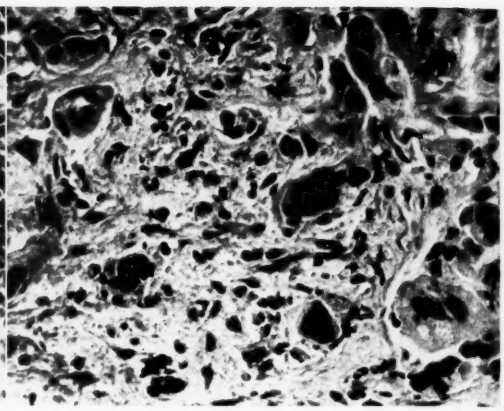

FIG. 4. Needle biopsy of liver showing metastatic carcinoma after marked regression of hepatomegaly coincident to chemotherapy. ×250.

followed by regression of the tumor masses and relief of the back pain.

She remained well until September 1954 when tumor recurrences were noted and herpes zoster of the thorax appeared. The herpes responded to cortisone therapy but the tumor continued to grow. She was readmitted to the hospital on September 20, 1954 at which time she was jaundiced. A biopsy of the skin nodules and a needle biopsy of the liver were taken (Fig. 5). The liver biopsy revealed metastatic carcinoma from the breast. From September 22 to 28, 1954 she received 10 milligrams of TEM and 18 milligrams of urethane. However, her condition continued to deteriorate and the jaundice increased progressively although marked sloughing of the skin nodules was noted. She expired on October 4, 1954. Authorization for postmortem examination was limited to the skin nodules and examination of the liver. Figure 6 depicts the findings in the skin and liver. It will be noted that there was extensive cytonecrosis of the tumor cells as well as nuclear gigantism.

This case illustrates the ability of urethane and TEM to produce striking although temporary subjective and objective benefits in a case of breast cancer. The posttreatment tissue examinations provided microscopic demonstration of the type of tumorcidal action associated with this form of therapy. This case also shows the correlation between the in vitro and in vivo effects of urethane plus TEM.

COMMENTS

The findings in the present series of breast cancer cases are of interest in regard to the biochemistry of cancer tissue as well as in regard to the clinical management of disseminated breast carcinoma. The in vitro measurements confirm our previous reports that breast cancer tissues from individual cases have decided variations in their metabolic activity (3, 4). In view of such biochemical variations it is not unexpected that wide variations in response to x-ray therapy and chemotherapy are encountered among individual cases of breast carcinoma. In this connection, it should also be mentioned that in a recent study we found variations in the effects of fluoride and azid on the in vitro dehydrogenase activity of human breast cancer tissue slices. In the latter studies a correlation was found between the biochemical measurements and the endocrine status of the patient (6). In the present study, however, no correlation was apparent between the biochemical measurements, the age of the patients, or the microscopic structural pattern of the tumor.

The observation that urethane and TEM may exert a synergistic action in producing an inhibition of the in vitro metabolism of breast cancer tissues is pertinent to the problem of cancer chemotherapy. These findings are even more striking in view of the in vivo observations of similar synergistic actions between urethane and TEM as demonstrated by

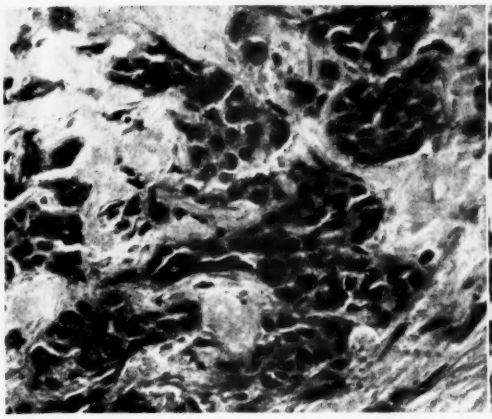

FIG. 5. Patient M. M. Needle biopsy of liver showing metastatic breast carcinoma before chemotherapy. ×250.

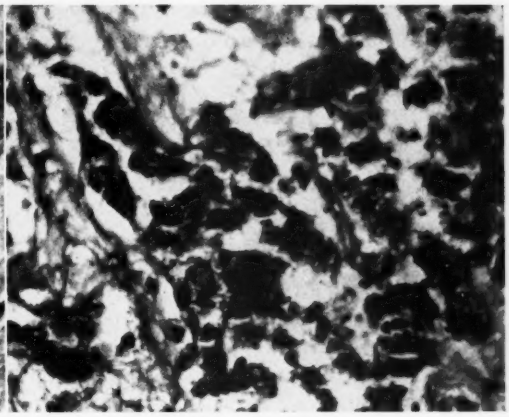

FIG. 6. Liver tissue removed at autopsy showing metastatic breast cancer after chemotherapy. ×250.

Skipper in experimental animals and our own studies in human cancer cases (5). Recently Innes and Rider have also reported on the use of urethane and on oral mustard (-naphthyl-di(2-chloropropyl)-amine) in the treatment of multiple myeloma. Their findings confirmed the existence of a synergism in antitumor activity between these two agents.

Despite the increased chemotherapeutic efficacy of the combination chemotherapy it should be realized that of the unselected cases only 4 experienced good objective and subjective benefits. Furthermore, such response was only temporary. While we found no evidence that the combination chemotherapy increased the toxicity neither did it eliminate it. It is, therefore, highly desirable that such chemotherapeutic procedures be reserved for those cases most likely to respond. The data obtained in this study are consistent with our previous observations that chemotherapeutic benefits are much more frequently encountered in those cases in which there was an appreciable inhibition of the in vitro dehydrogenase activity of the tumor slice by the agent or agents in question In this connection it is pertinent to note that of the 7 cases in which in vitro measurements were made, good therapeutic effects were observed in all 5 cases with in vitro inhibition greater than 40 per cent. In contrast, poor clinical responses were found in the 2 cases with in vitro inhibition less than 25 per cent. While our present report is concerned with observations on breast carcinoma it should also be mentioned that similar studies on other types of human carcinoma revealed similar correlation between in vitro and clinical effects. In the light of these data we believe that when it is practical, use should be made of such in vitro measurements in the selection of cases for chemotherapy with marrow toxic agents.

It is pertinent to note that in our previous studies we had found a correlation between in vitro urethane effects and the clinical response to x-ray therapy (3, 4). It might, therefore, be expected that a synergism would exist between x-ray therapy and mustard therapy. The current literature contains reports by Beecham and Bethell and their associates which would tend to confirm this conclusion. In those cases in which the dominant clinical problem is related to a relatively localized tumor mass, x-ray plus mustard therapy might be preferable to urethane plus mustard therapy.

It should be kept in mind that the use of these agents is not innocuous and careful attention should be paid to the hematologic status of the patients receiving such therapy.

While the in vitro and clinical demonstration of the possibility of enhanced benefits with combination chemotherapy in human cancer has opened an interesting avenue for further investigation, much more work is needed properly to evaluate its potentialities and place in cancer therapy.

SUMMARY

Measurements were made of the in vitro dehydrogenase activity of breast cancer tissues from 94 cases. Determinations were made of the effect of urethane and TEM singly and in combination on such in vitro metabolic activity. The findings indicated the existence of a synergistic action between urethane and TEM in producing inhibition of the in vitro metabolic activity.

The clinical effects of this chemotherapeutic combination was studied in 21 cases. In 7 of these cases both clinical and in vitro measurements were made. The data obtained indicated that urethane and TEM therapy was capable of producing striking clinical benefit in some cases of human breast cancer. Such beneficial effects appeared to be related to and predicted by the in vitro effects of these agents.

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HISTOLOGIC CHANGES IN THE UTERINE CERVIX DURING PREGNANCY AND THE DIAGNOSIS OF CARCINOMA IN SITU

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IN THE PAST 10 YEARS, numerous studies evaluating the nature, frequency, characteristics, and prognosis of carcinoma in situ have appeared. As yet there is no general agreement regarding the prognosis of carcinoma in situ. However, the following points are generally accepted: (1) Carcinoma in situ may become infiltrating. (2) This transformation from a noninfiltrating carcinoma may occur at any time, the average interval being between 5 and 10 years. (3) All cases of carcinoma in situ do not necessarily become infiltrating; some lesions may persist as such for a number of years and others may even disappear. (4) Since there is no way to establish its future evolution, as soon as a case of carcinoma in situ is diagnosed, it must be treated as if it were going to infiltrate.

It is well known that, in a certain proportion of pregnant women, changes in the cervical epithelium may occur which are difficult to distinguish, or are indistinguishable, from carcinoma in situ. Some authors have considered these epithelial alterations as transitory and claim that they disappear within a few weeks after childbirth. Others consider them permanent and classify them as genuine carcinoma in situ.

It is clear that the view one holds of the nature of these alterations in pregnancy affects the method of treatment. If one regards them as benign and self-limited, a conservative therapeutic attitude results. If, on the other hand, they are considered to be true carcinomas in situ, active treatment must be resorted to.

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It is the purpose of this study to present information on the incidence of these cervical epithelial changes in pregnancy, to compare these changes with those of carcinoma in situ, and to attempt to evaluate the evolution of such changes.

MATERIALS AND METHODS

A histologic study was made of cervical biopsies obtained on 200 pregnant women during labor or immediately after childbirth. As a rule, biopsies were taken from all quadrants of the cervix.

Analysis of the material revealed that, depending on the morphologic criteria outlined below, cases could be classified into four groups (Table I):

Group A. In group A the morphologic changes noted were similar or identical to carcinoma in situ and constituted atypical metaplasia of the endocervix. They consisted of disorganization of the normal cellular stratification, increase in the number and size of the nuclei, increase of the nuclear-cytoplasmic ratio, and the presence of grossly deformed and very large nuclei (Figs. 1, 2, 3, and 5). In addition, other alterations were sometimes found which are included in the following groups.

Group B. In group B the outstanding findings were hyperplasia of the basal cell layer and increase in the size of the nuclei, without the presence of atypical nuclei (Fig. 4). In addition, the alterations found in groups C and D were noted.

Group C. In group C there was a moderate hypertrophy of the ectocervical epithelium and hyperplasia of the basal cell layer. However, the hyperplastic zone did not exceed

TABLE I.—DISTRIBUTION OF 200 CASES BY GROUPS STUDIED ACCORDING TO THE ALTERATIONS FOUND IN THE CERVICAL EPITHELIUM

Groups	*No. of cases*	*Percentages*
A	18	9.0
B	17	8.5
C	75	37.5
D	90	45.0
Total	200	100.0

one-third of the thickness of the epithelial layer. The endocervix showed simple and adenomatous hyperplasia. There was moderate swelling of the cells with an increase of the vacuoles in the cytoplasm. In the stroma sometimes changes were found as described in group D.

Group D. In group D there were no characteristic epithelial changes. The stroma showed hyperemia, foci of hemorrhage, edema, chronic inflammatory infiltrations of variable extent, and, occasionally, decidual changes.

The criteria used in this study to define carcinoma in situ, atypical metaplasia, and atypical hyperplasia are those of Nolan and Pollak. All patients in groups A and B and 15 individuals in group C were re-examined 6 weeks after labor. There were no follow-up examinations of patients in group D. At re-examination repeat biopsies were taken and special emphasis was placed on the persistence, disappearance, or change in the nature of the previously observed cervical lesions. In those cases in which alterations were present on the second examination, a third series of biopsies was taken 4 or 6 weeks after the second examination.

TABLE II.—FREQUENCY OF EPITHELIAL ALTERATIONS FOUND IN GROUPS A AND B

	Group A (18 cases)		*Group B (17 cases)*	
Alterations of epithelium	*No.*	*Per cent*	*No.*	*Per cent*
Similar to carcinoma in situ	10	55.5	—	—
Atypical nuclei	18	100.0	—	—
Increase in size of nuclei	18	100.0	11	64.7
Hyperchromatism	18	100.0	2	11.7
Cellular disorder	18	100.0	2	11.7
Hyperplasia of the squamous epithelium	5	27.8	12	70.5
Hyperplasia of the basal layer	18	100.0	14	82.3

RESULTS

The 200 cases studied were grouped according to age, race, and number of pregnancies, but none of these variables was related to the incidence of the following histologic changes.

HISTOLOGIC FINDINGS

Hyperplasia of the ectocervical epithelium. The squamous epithelium of the ectocervix was increased in thickness in 27.8 per cent of the cases in group A, 70.5 per cent of those in group B, 53.0 per cent of those in group C, and only 4.0 per cent of the cases in group D. The degree of hyperplasia of the epithelium was always much greater in groups A and B than in group C. Hyperplasia of the ectocervical epithelium is a lesion which frequently accompanies chronic inflammatory processes of the cervix in nonpregnant women. However, the relatively high percentage found in the present series of cases leads us to think that pregnancy accentuates the appearance of this lesion. It may be that the frequency of this change in pregnancy is correlated with the high estrogen level, as pointed out by Hellman and co-workers (Tables II and III).

Hyperplasia of the basal cell layer. This change was found in 63.0 per cent of the cases. It is apparent that the presence of this lesion is related to pregnancy, for in patients examined 6 weeks after delivery, its incidence had declined to 18.1 per cent. Hyperplasia of the basal cell layer is also related to estrogenic activity and is seen in nonpregnant women during periods of relatively high estrogen levels.

Loss of cellular stratification. This change was found in 20 cases (10.0 per cent), most of them in group A, and was always associated with other epithelial changes, such as hyperplasia of the basal cell layer, nuclear hyperchromatism, and increase in the number and size of the nuclei. In these cases the cells lost the ordinary polar orientation of the single layered epithelium of the endocervix, and the nuclei disposed themselves in arrangements which produced an appearance

TABLE III.—SUMMARY OF THE HISTOLOGIC FINDINGS IN THE BIOPSIES TAKEN DURING DELIVERY AND 6 AND 12 WEEKS AFTER DELIVERY IN EACH OF THE GROUPS DESCRIBED

	Biopsy during delivery, per cent					*Biopsy after 6 weeks, per cent*			*Biopsy after 12 weeks, per cent*		
Cervix	*A*	*B*	*C*	*D*	*Total*	*A*	*B*	*C*	*A*	*B*	*C*
Epithelium											
Basal cell hyperplasia	100	82.3	92.0	—	63.0	35.2	25.0	13.3	16.6	—	—
Increase in size of the nuclei	100	64.7	—	—	14.5	23.5	—	—	—	—	—
Cellular disorder	100	11.7	—	—	10.0	33.3	—	—	—	—	—
Hyperchromatism of the nuclei	100	11.7	—	—	10.0	5.1	—	—	—	—	—
Atypical nuclei	100	—	—	—	9.0	—	—	—	—	—	—
Resembling carcinoma in situ	55.5	—	—	—	5.0	—	—	—	—	—	—
Resembling infiltrating carcinoma	22.2	—	—	—	2.0	—	—	—	—	—	—
Squamous epithelial hyperplasia	27.8	70.5	53.0	4.0	30.5	11.1	11.7	13.3	—	—	—
Epidermoid metaplasia	77.8	35.2	18.6	10.0	25.5	22.2	35.2	13.3	—	—	—
Stroma											
Decidual changes	11.1	5.9	8.0	13.3	10.5	—	—	—	—	—	—
Cervicitis	33.3	58.5	52.0	85.5	65.0	66.6	35.2	52.0	44.4	35.2	52.0
Congestion and edema	61.1	64.6	62.7	58.9	60.0	22.2	35.2	18.6	—	—	—
Hemorrhage	—	11.7	5.3	8.9	7.0	—	—	—	—	—	—
Glands											
Nabothian cysts	16.7	17.6	66.0	42.2	35.5	22.2	17.6	—	16.7	11.7	—
Glandular hyperplasia	22.2	11.7	2.7	14.4	10.5	11.1	11.7	—	—	—	—

of pseudostratified epithelium (Figs. 1, 4, 3 and 5).

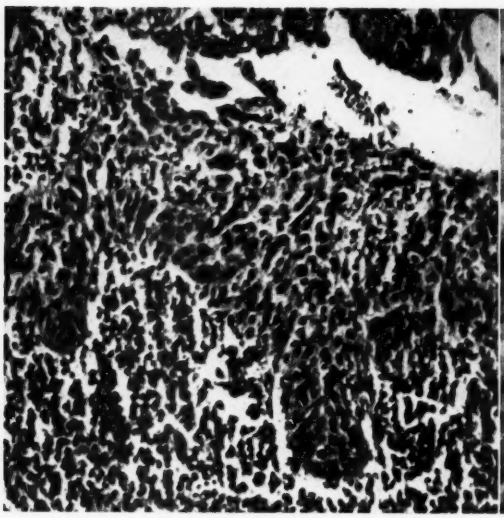
Increase in size of the nuclei. Twenty-nine cases (14.5 per cent) showed an increase in the size of the nuclei of the squamous epithelium of the ectocervix or endocervix. Eighteen of these cases (9.0 per cent) were in group A, and this lesion was usually associated with cellular disorder, hyperplasia of the basal cell layer, and the presence of atypical cells. However, postpartum biopsy showed that this lesion persisted in only 4 cases after 6 weeks and was completely absent in all after 12 weeks (Tables II and III), (Figs. 2 and 3).

Nuclear hyperchromatism. This change appeared in the nuclei of the cells of the endocervix in 20 cases (10.0 per cent), 18 in group A and 2 in group B (Tables II and III). This lesion was also associated with hyperplasia of the basal cell layer, atypical nuclei, disordered cellular stratification, and increase in the size of the nuclei (Figs. 2, 3, 4, and 5). In only 1 case was the hyperchromatism present 6 weeks after delivery, and after 12 weeks it was not present in any case. We therefore consider this change a transitory one dependent upon pregnancy.

Atypical nuclei. Atypical nuclei were found in 18 cases (9.0 per cent) and generally involved the endocervical canal and glandular epithelium; in 3 cases this condition was present also in the ectocervical epithelium. This change consisted of deformity of the nucleus and increase of the nuclear volume, and in some cases resulted in the appearance of nuclear gigantism (Figs. 2 and 3). The nuclei were prominent and variable in number. The chromatin was arranged in thick nets or compact masses with an increased affinity for hematoxylin.

Changes associated with this lesion included marked cellular disorder and hyperplasia of the basal cell layer (Tables II and III). In a follow-up study at 6 and 12 weeks after delivery, these changes were absent, and we, therefore, attribute this lesion also to pregnancy.

Histologic changes of the cervix during pregnancy similar to carcinoma in situ. In 10 women (5.0 per cent) the alterations of the epithelial morphology were exactly similar to those of carcinoma in situ. In 4 of them (2.0 per cent) there was suggestive incipient infiltration into the stroma. This condition was noted in the endocervix and was localized to one or two fields. It was thought that actual infiltration into the stroma was not occurring, but that the stromal changes previously described (edema and inflammatory infiltra-



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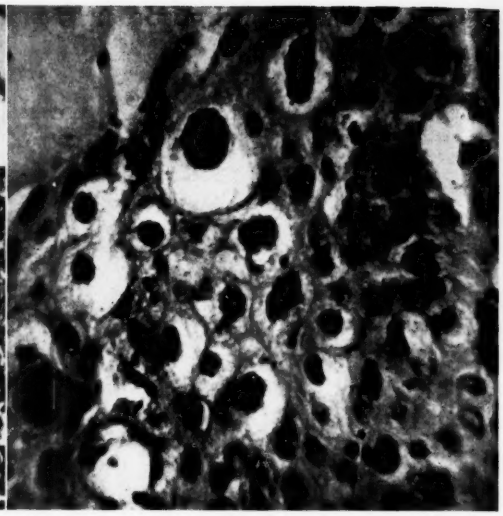

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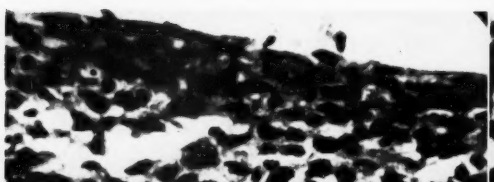

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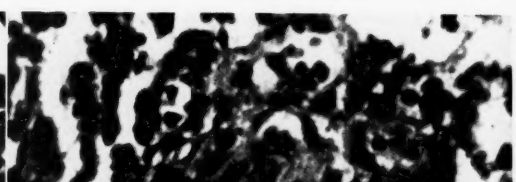

FIG. 4.

FIG. 1. Endocervical biopsy during delivery. Note alterations suggestive of a very early infiltrating carcinoma.

FIG. 2. Basal epithelium of the portio. Note increase in size and chromatism of nuclei, with some atypical cells.

FIG. 3. Epithelium of the portio. Note similarity to carcinoma in situ.

FIG. 4. Note the focus of squamous metaplasia below the endocervical gland. A tripolar mitosis is also present.

tion) were responsible for this appearance (Fig. 1).

Originally we were uncertain as to whether, in these cases, a true carcinoma in situ was present, and this large percentage made us decide that we were probably not dealing with a true carcinoma in situ. In addition, since a follow-up of these patients never showed any changes at 6 and 12 weeks after pregnancy, we concluded that these changes were entirely due to pregnancy (Figs. 5, 6, and 7).

Decidual changes. These changes were present in 21 cases (10.5 per cent), equally dis-

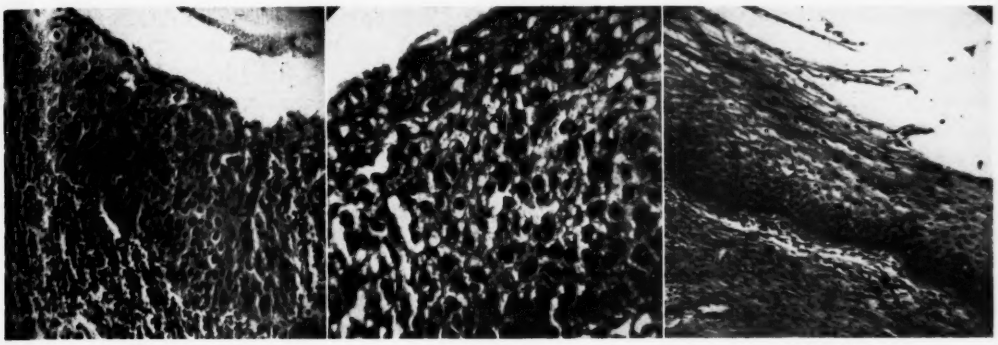

FIG. 5. FIG. 6. FIG. 7.

FIGS. 5, 6, and 7. A case of group A. Biopsies at delivery, 6, and 12 weeks. Progressive reversion to normality is evident.

tributed among all the groups. The decidual reaction was entirely absent at the time of the second examination in all cases (Table III).

DISCUSSION

A review of the literature on cervical epithelial changes during pregnancy and their relationship to carcinoma in situ reveals considerable variation of opinion. Epperson and associates, in a study of 286 cases, found lesions which they classified as "intraepithelial carcinoma" in 5 cases (1.74 per cent). They advanced the view that these changes were produced by pregnancy and that they were not true carcinomas. Nesbitt and Hellman studied 300 pregnant women and found 2 cases of "carcinoma" and 3 of "cellular anaplasia," an incidence of 0.6 and 1.0 per cent respectively. Twenty cases of hyperactivity of the basal cell layer were also found. Follow-up examination at 6 months revealed that all of these lesions had disappeared. The authors, therefore, concluded that none of these cases represented a true carcinoma and that all the changes were attributable to pregnancy. Brown and Jernigan found 5 cases in which the cervical epithelium showed atypical nuclei during pregnancy. In 2 of these cases, these changes disappeared after delivery. Hahn, quoted by Epperson, found 1 case of "carcinoma" which disappeared after delivery.

On the other hand, Greene and associates (4, 5) found 14 cases which they classified as "preinvasive carcinoma." In 2 cases this lesion disappeared after delivery; however, in the other 12 cases it persisted after labor. The conclusion drawn was that these lesions were not the result of pregnancy alone. Peckham and associates (10, 11) continuing this series, added 5 cases to the 14 described by Greene and co-workers. In 4 the "carcinoma" persisted between 8 and 37 weeks after delivery. Combining these figures, 19 cases of "carcinoma" were found in a series of between 10,000 to 15,000 pregnant women, resulting in percentages of 0.13 to 0.19 per cent of the cases. In 16 of these 19 cases the changes resembling carcinoma in situ persisted after delivery. Peckham and associates (10, 11) in a third study of the same group of women, described other minor abnormalities in the cervical epithelium. Essentially these consisted of atypical basal cell hyperplasia which occurred definitely in 5 cases and which were regarded as questionable in 14 others. Those cases considered as doubtful resembled atypical metaplasia.

Of these 19 patients with "carcinoma," 6 returned to normal; improvement occurred in 2 others; and the lesions persisted or progressed in the remaining 11. Again, these authors advanced the view that such alterations of cervical morphology in pregnancy are not caused by pregnancy and that the

majority of their cases were instances of true carcinoma in situ.

Our own observations showed that: (1) Certain epithelial changes, such as squamous metaplasia, hyperplasia of the basal cell layer of the ectocervical epithelium, and glandular hyperplasia, are more frequent in pregnant than in nonpregnant women, confirming the work of Epperson and associates, Glass and Rosenthal, Nesbitt, and Nolan and Pollak. (2) Those lesions which are morphologically similar to carcinoma in situ and which may be confused with carcinoma in situ, i.e., epithelial hyperplasia or atypical metaplasia, are transitory changes which occur during pregnancy and disappear in the postpartum period.

In our series, the frequency of these changes is higher than may be judged from the literature. We do not know if this fact is due to differences in the histologic interpretation or in the population examined.

Though the changes described in detail can reasonably be ascribed to the effect of pregnancy, it is possible that genuine cases of carcinoma in situ appear during pregnancy. Our series, and that of Epperson and Nesbitt and Hellman consisted of relatively few cases, so that there is the possibility that no genuine case of carcinoma in situ was discovered, since the incidence of infiltrating carcinoma of the cervix in pregnancy (according to Rosende quoted by Hirst) is 0.34 per cent. Those authors whose statistics are based on more material, notably Peckham (10, 11) and his coworkers, may thus have more opportunity to find genuine cases of intraepithelial carcinoma. But even these authors observed that in some instances the cervical alterations thought to be carcinoma in situ disappeared in the postpartum period.

From these observations, it is clear that it is difficult, or perhaps impossible, to diagnose carcinoma in situ in pregnant women with any degree of certainty. To clarify such cases, it is necessary to take repeated biopsies in the postpartum period in order to have a rational basis for correct therapy.

SUMMARY

1. A study of the histologic structure of the cervices of 200 pregnant women was made by means of multiple biopsies before or immediately after labor. If abnormalities were present, repeat biopsies were taken at 6 and 12 weeks after labor.

2. The histologic lesions observed are described in detail.

3. In 10 cases (5.0 per cent), the histologic alterations were indistinguishable from those of carcinoma in situ. However, in all cases, these alterations had disappeared by the twelfth postpartum week.

4. It is concluded that alterations in the cervical morphology during pregnancy are the result of pregnancy per se.

5. It is pointed out that it is difficult, or impossible, to diagnose carcinoma in situ during pregnancy with certainty, and that, to distinguish carcinoma in situ from transitory changes due to pregnancy, prolonged follow-up after delivery is essential.

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ARTIFICIAL BLADDER FROM SEGMENT OF STOMACH AND STUDY OF EFFECT OF URINE ON GASTRIC SECRETION

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IN THE INSTANCES when it has become necessary to find a substitute bladder or to divert the urinary flow, no method has been found satisfactory. In those cases in which the ureters have been transplanted to the colon, deleterious chemical changes, like acidosis, hyperchloremia, azotemia, and hypokalemia, have ensued because of renal failure from infection ascending the urinary tract from the colon. Lloyd and Baumrucker reported "transplantation of the clean ureter into the dirty bacteria laden bowel results in inevitable, ultimate, pyelonephritis in a high percentage of cases, regardless of the skill of the operator or the technique employed. Cutaneous transplantation of the ureter is far safer. It is, however, messy, difficult to take care of, and not devoid of complications . . . including decubitus from the indwelling catheter with resulting stricture, pyelonephritis, calculus formation and periureteral abscess. Where no catheter is employed, stricture of the ostium may cause trouble." Rolnick has also stated that both skin ureterostomy and ureterosigmoidostomy are unsatisfactory because of the sequelae which ensue. Both Lloyd and Baumrucker and Matern stated that after ureterosigmoidostomy electrolyte imbalance was not uncommon and was as inevitable as the pyelonephritis, which by itself was a factor producing it. Ferris and Odel noted hyperchloremic acidosis in 79 per cent of 141 cases, due to intestinal absorption of chlorides, and treated with high sodium, low chloride diet. Lapides found urographic abnormalities and electrolyte imbalance after ureterosigmoidostomy in 77 per cent of 23 cases, following recurrent acute pyelonephritis. He believes, that pyelonephritis is the primary factor in this imbalance, and that absorption of urine is secondary. Pool and Cook have observed urographic changes as early as 6 months postoperatively. Hypokalemia and acidosis in cases of ureterosigmoidostomy has been described by Albright as being due to "tubular insufficiency without glomerular insufficiency, with decreased ability of the kidneys to conserve potassium."

Lloyd and Baumrucker view the presently used urinary diversion techniques pessimistically. Some of their surgical patients never recovered from electrolyte imbalance and died in uremia. Even those who recovered often suddenly collapsed, became stuporous, and died in uremic coma. In 10 out of 14 autopsies, pyelonephritis was a major or a contributing cause of death. An analysis of their cases showed few 5 year survivals, with the greatest mortality in the first year, occurring even in patients who were considered to be good risks. So strongly do these authors feel about their results, that they propose conservative and palliative rather than radical treatment for carcinoma of the bladder. Palliative and conservative treatment, they believe, may offer a longer and a more comfortable life and should be used until such time when a satisfactory method of diversion of the urine can be devised.

In paraplegics, hydronephrosis and reflux of urine from the bladder occurred in 66 per cent, and hydronephrosis without evidence of stones or of obstruction in 5 per cent of cases. Skin ureterostomy has been advised in the cases with severe hydronephrosis, but the sequelae were as bad as in the other cases, in which ureterosigmoidostomy was employed. Bricker has used an isolated ileal segment as a substitute urinary bladder. In

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This study was supported by A. M. A. Grant No. 71.

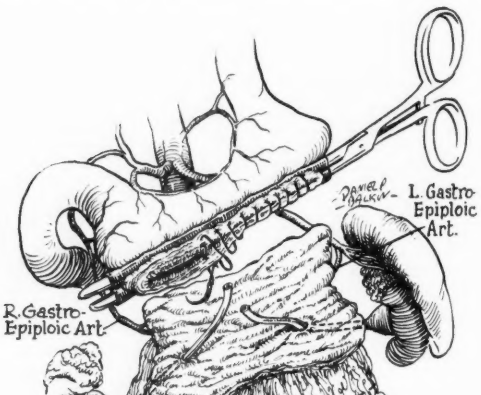

FIG. 1. Closure of main stomach. Open pouch with both ureters introduced.

28 patients, within 6 to 22 months, 8 have developed pyelonephritis, and 70 per cent of the total of 55 transplants studied have been found normal or to have only minimal hydronephrosis. Several of his patients, however, were found to have some elevation of plasma chloride. Of all the methods using segments of the intestine reported in the literature, only the method of Gilchrist and associates (4) and subsequently reported by Merricks and Gilchrist (8) shows promise.

In the solution of the problem of transplantation of the ureters, an isolated pouch made from a part of the stomach seemed to fill the criteria for a bladder substitute as:

1. The stomach mucosa is practically nonabsorbing, obviating the changes in blood chemistry when bowel is used.

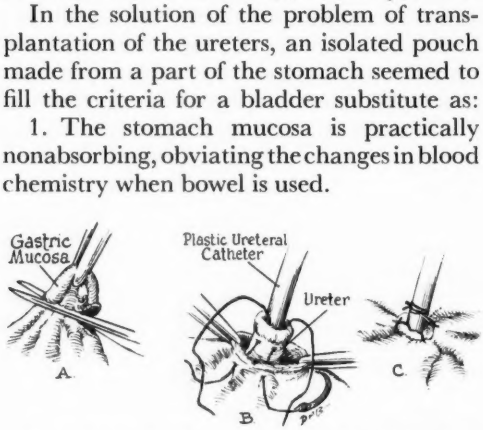

FIG. 2. Method of implanting ureter into Heidenhain pouch.

2. The low hydrogen ion concentration of the stomach and the gastric lysozyme constitute a physiologic bactericidal and bacteriostatic barrier which normally protects the small intestine against infection and which would prevent ascending infection of the kidneys.

3. In dog and man, excess stomach tissue beyond the needs of the animal is available for use as an artificial urinary bladder. It has been our experience that, after utilizing a portion of the stomach for a Heidenhain pouch or for the artificial bladder, the remainder of the stomach has eventually regained its original size, shape, and function.

4. The length of the ureter is more than sufficient to reach the pouch easily. We have learned to use only a proximal portion of its length for the anastomosis, thus minimizing the chance for constricting adhesions to form along its course.

5. It may be possible to produce a sphincter at the orifice of the pouch, resulting in a continent bladder substitute and only periodic catheterization.

6. Cystoscopic studies may be easily performed.

As our experiments progressed, the following questions arose:

1. Would loss of hydrochloric acid from the stomach pouch produce hypochloremia?

2. Would contact of urine with the mucosa of the gastric pouch stimulate acid secretion of the main stomach? Although the Heidenhain pouch is not vagus innervated, the gastrin mechanism would remain if even a small portion of the antrum was included in the pouch.

3. Would the urinary tract remain free of infection?

4. Would acid from the pouch regurgitate and damage ureters and kidneys?

PROCEDURE

Normal male and female mongrel dogs were operated upon aseptically under nembutal anesthesia. The kidneys and ureters were exposed through a midline incision. Each ureter was seized with thumb and fore-

finger through a fold of posterior parietal peritoneum, the overlying peritoneum was incised, and the ureter was freed. The spermatic or the ovarian arteries were carefully avoided. The ureters were cut between clamps near their junction with the urinary bladder, and the distal stump was ligated. The ureters were wrapped in a wet pack and put aside.

Next, a large Heidenhain pouch was formed out of the major portion of gastric fundus and corpus. The right and left gastroepiploic blood vessels were spared (Fig. 1). The main stomach was closed in two layers. Two small pieces of mucosa of the open pouch, somewhat to each side of its center, were picked up with a forceps and excised with scissors (Fig. 2A). The edges of each defect were picked up with 3 equally spaced small hemostats, and another hemostat was pushed through the center of the defect and through the entire wall of the stomach to pick up the end of each ureter. These were drawn through the defect until slight tension was felt, then relaxed, and most of the ureter protruding into the pouch was excised. A plastic catheter was introduced into each ureter, until the tip was palpable in the renal pelvis. Three chromic catgut No. 00 stitches were placed through the entire thickness of the ureter wall and the gastric mucosa at each of the previously placed hemostats (Fig. 2B). When the sutures were tied, they caused the mouth of the ureters to gape. The sutures were cut short except one, which was tied around the ureteral catheter, holding it in place (Fig. 2C). A seromuscular stitch was placed between the serosa of the stomach tissue and the adventitia of each ureter.

The ends of the ureteral catheters, by now filled with urine, were led through a flanged brass cannula (Fig. 3). Then the pouch was closed with two layers of catgut, including the cannula. The end of the cannula was brought to the outside through a stab wound in the abdominal wall, and the abdominal incision was closed. The ureteral catheters were cut off at the end of the cannula, so

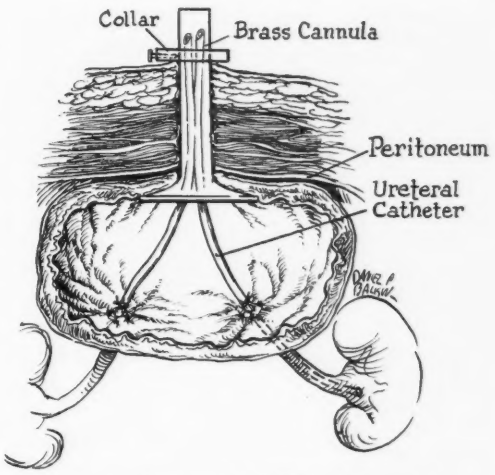

FIG. 3. Cross section of Heidenhain pouch.

that the dog would not be able to pull them out prematurely. Usually, the catheters came out spontaneously after 1 week. In those instances in which secretion studies were made, the operative procedures were performed in stages.

A number of dogs were operated upon for the development of the technique and are not reported here. In the following 5 dogs, standardized techniques were used, and the results obtained are described.

In dogs 1 and 2, a one stage operation was performed. In dog 3, a Heidenhain pouch was made first, and its secretion was studied. Following this, one ureter was transplanted into the pouch, and the effect of urine on pouch secretion was studied; also, simultaneous samples of urines from the urinary bladder and from the pouch were studied and they were found to be normal. In dogs 4 and 5, secretion of the Heidenhain pouch was studied first, followed by transplantation of both ureters and further studies.

INDIVIDUAL STUDIES

DOG 1. Male, 14 kilograms, a Heidenhain pouch, into which both ureters were transplanted. Operation was performed on May 25, 1953. Postoperatively, blood chlorides were 24.5 milliequivalents, blood hydrogen ion concentration was 7.8, pouch fluid hydrogen ion concentration was 2.0, and the skin at the

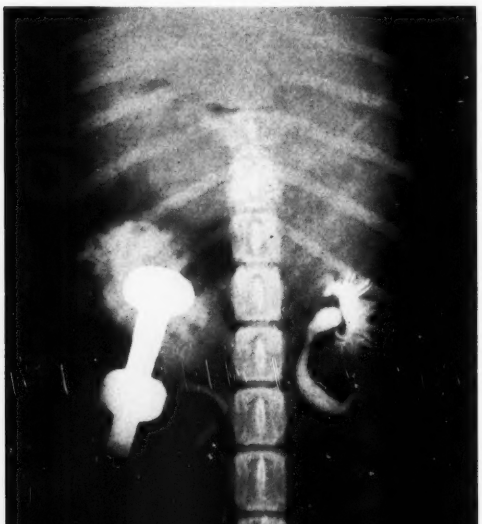

FIG. 4. Intravenous pyelogram, dog 2. Normal renal and ureteral configuration; no hydronephrosis; slight stenosis in the course of the left ureter probably due to adhesions. Artificial urinary bladder shown.

stoma of the pouch was excoriated. The low plasma chloride was probably due to postoperative depletion of chloride with retention of sodium and subsequent alkalosis, as Van Slyke and Evans have described. Feeding of sodium chloride corrected this, and after 5 grams of sodium chloride per os, the hydrogen ion concentration of the pouch fluid rose to 4.9 and that of the blood dropped to 7.6. We were certain that no excessive chloride loss through the pouch had caused the alkalosis but rather the hypochloremia was due to a fault in chloride replacement postoperatively. Following this episode, normal levels of urea, creatinine, and chlorides were present. No muscular weakness, such as Matern has reported following ureterosigmoidostomy, indicating potassium deficiency, was observed.

On October 20, 1953, intravenous pyelography was performed and a functioning right and a nonfunctioning left kidney were seen. Upon reoperation, the right kidney appeared normal, and the right ureter was of normal size, showing peristaltic waves on stimulation. The left renal pelvis and the proximal one-half of the ureter were dilated, due to an adhesion which constricted the ureter completely. The constricted end of the ureter was freed and resected, and a new ureterogastrostomy to the pouch was made. Urine began to flow, and ureter and renal pelvis decreased in size immediately. The main stomach was found to have enlarged to about normal size.

Following this experience, we used as short lengths of ureter as possible, to reduce the hazard of obstruction by adhesions.

The subsequent clinical course of this animal was normal. It developed a good appetite, gained weight, and was kept on no special therapeutic regime. On July 28, 1954, approximately 14 months after the first operation and 9 months after the second, intravenous pyelograms were taken. They showed normal functioning kidneys and ureters and an artificial bladder whose large capacity was demonstrated by closing the brass cannula.

The animal was killed accidentally. Autopsy disclosed normal kidneys and ureters and a well functioning ureterogastric pouch anastomosis. The main stomach was of normal size, its mucosa normal.

Thus, in this dog, the use of a segment of stomach as an artificial urinary bladder had been feasible. There had been little or no disturbance in blood chemistry following the episode of postoperative alkalosis, and kidneys and ureters were normal after a survival period of almost 15 months.

DOG 2. Male, 14 kilograms. In December, 1953, the same operation was performed as on dog 1. The animal recovered quickly and was in good health until his death from pneumonia 15½ months postoperatively. Postoperatively and until his death, blood chemistry studies demonstrated little or no change.

Intravenous pyelography on January 13, 1954, July 28, 1954, and January 12, 1955 showed normal renal and ureteral configuration, no hydronephrosis, and normal excretion of urine. There was a slight stenosis in the course of the left ureter, probably due to adhesions, but the flow of urine evidently was not obstructed, and the pelvis of the left kidney showed no hydronephrosis. The pyelogram of January 12, 1955 is shown in Figure 4. Both kidneys, pelves, and ureters are visible. The artificial bladder is seen, because the cannula has been plugged and the pouch had filled with urine. The normal pyelogram is indicative of and consistent with normal histology of the kidney.

Figure 5 is a photograph of both kidneys, ureters, and the opened artificial urinary bladder removed at autopsy. A portion of the anterior abdominal wall is seen with the brass cannula in situ. It will be noted that both kidneys and ureters are normal in size and configuration. Probes mark the patent openings of the ureters into the artificial urinary bladder.

Dogs 3, 4, and 5 had Heidenhain pouches, and the ureters were transplanted in two stages in order that secretion of the pouches and of the kidneys could be studied before and after transplantation.

Dog 3. Male, 23 kilograms, April 5, 1954, Heidenhain pouch. On April 7, 1954, urea nitrogen was 14.8 milligrams per cent, creatinine 1.4 milligrams per cent, chlorides 187.1 milliequivalents (blood chlorides in the dog are normally somewhat higher than in man). The basal secretion of the pouch was studied 4 times at 3 day intervals. Secretion was collected at 15 minute intervals for 5 hours. Secretion was scanty, from 0 to 2 milliliters per hour; free acidity was either zero or present, but was not titrated due to the small quantities of fluid. Following the secretion studies, the effect of irrigation of the pouch with fresh dog's or human urine was investigated in the starved animal. Approximately 100 milliliters of urine were instilled into the pouch without pressure and left there for 20 minutes. Following complete drainage, pouch secretion was collected for 5 hours. The volume varied from 0 to 1 milliliter per 15 minute period, and free acid was absent. Thus, it seemed that urine had no appreciable stimulating effect upon pouch secretion.

The left ureter was transplanted into the pouch on May 25, 1954. Following recovery, and with good evidence that the transplanted ureter was functioning, observations on volume and hydrogen ion concentration of pouch secretions were made on the fasted animal on June 3, 1954. The volume of fluid from the pouch per 15 minutes was between 0 and 2 milliliters, with a hydrogen ion concentration between 6.7 and 7.5. This observation confirmed the experience related before that urine applied locally to the mucosa of a Heidenhain pouch does not stimulate secretion.

The effect of feeding on the secretion of the pouch was tested. Following a control period, the dog received a mixed meal, and secretion was collected for 5 hours. The volume increased up to 5 milliliters per 5 minutes, but the hydrogen ion concentration did not fall below 7.2. Therefore, histamine was given in subsequent experiments, in order to test the functional capacity of the pouch to secrete hydrochloric acid. One-half of a milligram of histamine base was given subcutaneously, and secretion was collected for 2 hours. Volumes went up to 6 milliliters per 15 minute periods, and hydrogen ion concentration decreased to as low as 1.14, indicating good functional responsiveness to a strong stimulus.

Dog 4. Male, 11.5 kilograms. Control blood chemistries were: urea nitrogen 26.4 milligrams per cent, creatinine 1.35 milligrams per cent, chlorides 190 milliequivalents. On April 12, 1954, a Heidenhain pouch was formed. Upon recovery, studies were made on basal pouch secretion, the effects on pouch secretion following irrigation of the pouch with the dog's own urine, and a study on the effects on pouch secretion of placing a volume of urine into the main stomach. The basal pouch secretion varied between 0 and 0.1 milliliter per 30 minute period, with no free acid. Following irrigation of the pouch with urine, its secretion was similar to the basal secretion. The introduction of 200 milliliters of human urine into the main stomach by tube did not affect pouch secretion. It was evident, therefore, that urine in the pouch or in the main stomach did not provoke the gastrin nor other stimulating mechanisms for pouch secretion.

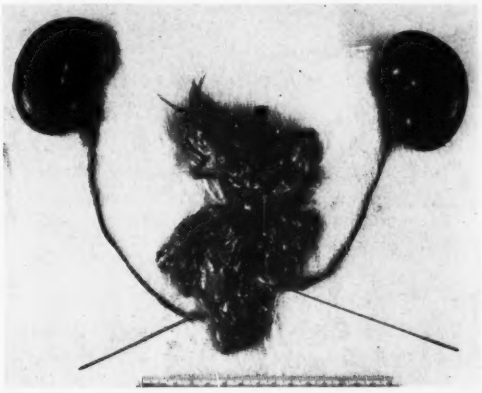

FIG. 5. Autopsy specimen, dog 2, 15½ months after operation, showing normal kidneys and ureters. Probes mark the patent openings of the ureters into the artificial urinary bladder. Also shown is a segment of abdominal wall and brass cannula in situ.

On June 7, 1954, the dog was reoperated upon and both ureters were transplanted into the pouch. On June 21, 1954, pouch studies were made on the fasted animal. Volumes of fluid up to 7.5 milliliters per 30 minute period were obtained, with hydrogen ion concentrations varying between 6.6 and 7.9, and with no free acid present. The effect of mixed food on pouch secretion was tested. Volumes up to 15 milliliters per 30 minutes were collected, with hydrogen ion concentrations varying between 1.9 and 5.8. Following subcutaneous injection of 0.5 milligram of histamine base, volumes up to 17 milliliters per 30 minute period were obtained, the hydrogen ion concentration dropping from 7.9 to 3.5. Chemical studies on December 1, 1954 indicated normal values for blood urea nitrogen, creatinine, and chlorides.

Dog 5. Male, 18 kilograms, May 3, 1954, Heidenhain pouch. On June 10, 1954, a control study was made on the transplanted pouch for six 30 minute periods. Volumes per period were between .05 and .5 milliliter with no free acid. On June 14, 1954, both ureters were transplanted into the pouch, and on June 29, 1954, studies on the pouch were made. The results indicated a good volume of urine during the 300 minutes of observations with the hydrogen ion concentration of the mixture of urine and gastric secretions dropping to 5.8. On July 1, 1954, the effect on pouch secretion of a meal of mixed dog food was tested. This stimulation was sufficient to lower the hydrogen ion concentration of the pouch fluid within

1 hour to 3.6, and to increase volumes significantly. On July 2, 1954, fluid from the pouch following administration of histamine was studied. The stimulation of the pouch by histamine was sufficient to lower the hydrogen ion concentration of the pouch fluid within 1 hour to 1.48.

The dog lived in apparently good health until July 26, 1954, when it died suddenly. Autopsy disclosed a left hydronephrosis and hydroureter due to stenosis of the left ureter by adhesions. The right ureter and the right kidney were normal.

CONCLUSIONS

1. In the dog, the use of a Heidenhain pouch as an artificial urinary bladder is practicable and is compatible with life.

2. When hazards, like kinking of a ureter or stenosis of the ureterogastric anastomosis, are avoided or corrected, a dog with bilateral ureteral transplants into a Heidenhain pouch may possibly live indefinitely and in good health.

3. In some dogs still living and in dogs studied for as long as over 15 months, there was an absence of hyperchloremia or hypochloremia, acidosis or alkalosis, uremia, and no clinical evidence of hypokalemia. This observation indicates little or no absorption of urine from the pouch and an absence of ascending pyelitis or pyelonephritis.

4. Normal pyelograms and normal secretion of urine were seen in these representative dogs, indicating normal renal structure and function.

5. Normal blood chloride levels indicate a negligible loss of chloride from the Heidenhain pouch.

6. Urine introduced into the pouch or into the main stomach did not affect pouch secretion.

7. The Heidenhain pouch responds to stimulation by food and histamine with increased acid secretion.

8. Periodic flushing of the artificial bladder with acid gastric juice plus lysozyme activity, certainly at time of food ingestion, appears to act as bacteriostatic and bacteriocidal agents preventing ascending infection of the kidneys.

9. It is believed that this method is applicable to the human.

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CHRONIC RECURRENT BREAST ABSCESS SECONDARY TO INVERSION OF THE NIPPLE

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CHRONIC RECURRENT ABSCESS of the female breast can be a difficult surgical problem. The origin of these abscesses may be obscure. Those abscesses which begin in the lactating female can be explained on the basis of bacterial invasion, usually staphylococcus, via the nipple. Frequently, however, the initial episode of infection occurs in the nonlactating female without any history of antecedent trauma or infection. Chronic tuberculous abscess of the breast is unusual, and this diagnosis is not difficult in most instances in that there is usually evidence of significant tuberculosis involving other systems.

These patients with recurrent pyogenic abscesses frequently have a history of multiple incisions and drainages over a period of months to years without cure. The dense fibrofatty compartments of the breast lend themselves poorly to adequate drainage, and in many cases surgical excision of the involved area under antibiotic protection is required. The results of this procedure have been generally satisfactory. Simple mastectomy has been done on occasion for control of these recurrent infections, but should rarely be necessary in the "sulfone-antibiotic era."

Zuska, Crile, and Ayres have reported 5 patients with comedomastitis in whom chronic periareolar abscesses developed secondary to ductal infection in the subareolar region with localization and drainage through the periareolar area. Kilgore and Fleming likewise attest to the role which the infected duct can play in recurrent breast abscess. Both of these authors emphasize the need for surgical excision of the involved duct in the treatment of these chronic abscesses.

During the past 2½ years, we have observed 6 patients with chronic recurrent periareolar breast abscesses. The duration of their disease varied from 2 to 20 years. All of these patients had a history of congenital inversion of the nipples. Exploration of the chronic abscess cavity revealed a connection with the "groove" of the inverted nipple in each instance. In 5 of these patients, this tract could be demonstrated without anesthesia (Figs. 1, 2, and 4).

It would appear that the origin of the chronic abscesses in these 6 patients was originally on the basis of maceration and cellulitis involving the cutaneous and glandular structures in the "groove" of the inversion of the nipple. A subareolar abscess then developed which loculated in the periareolar region. Recurrent episodes of infection occurred despite multiple incisions and drainages due to the persistence of the nipple inversion. Five of these 6 patients had pathologic examination of the removed tissue. In 4 of these, there was no histologic evidence of ductal or acinar breast involvement to a significant degree. In 1 patient, a large ductal structure was involved.

Treatment consisted of elliptical excision of the sinus tract, including the overlying skin and involved subcutaneous tissues, through the areola into the base of the inverted nipple. The wound was then closed, either partially or completely, with interrupted vertical mattress alloy-steel wire sutures which resulted in satisfactory correc-

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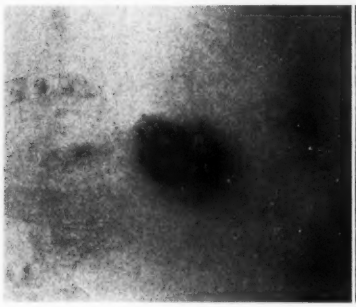

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 1. Chronic recurrent periareolar abscess of 20 years' duration with congenital inversion of the nipple (Case 5).

FIG. 2. A probe demonstrates the sinus tract between the chronic abscess and the inverted nipple (Case 5).

FIG. 3. Postoperative photograph showing correction of the inversion and absence of infection (Case 5).

tion of the nipple inversion (Figs. 3 and 5).

All 6 patients have been free of recurrent breast infection for periods of time varying from 8 to 30 months following the surgical treatment mentioned.

CASE REPORTS

Following are the reports on the 6 patients presented:

CASE 1. Mrs. M. R., a 35 year old female, was first seen in February 1953, with a chronic abscess of the right breast. The patient stated that she had always had bilateral inversion of the nipples. She had had her initial episode of breast infection 12 years previously and had had 2 recurrences since that time. Three months prior to examination she had noted another recurrent inflammatory episode involving the right breast, and this had required surgical drainage. A chronic abscess had persisted to the time of examination.

Examination revealed bilateral inverted nipples with a chronic breast abscess in the periareolar region on the right. This abscess was excised in February 1953, without any effort being made to correct the inversion of the nipple. It was not recognized that there was a connection between the abscess cavity and the depths of the inversion. The abscess promptly recurred and required additional drainage. However, at this time it was discovered that there was a sinus tract between the groove of the inverted nipple and the abscess cavity. Excision of the sinus tract with correction of the inversion of the nipple were then carried out in June 1953. Pathologic examination of the involved tissue revealed chronic inflammatory changes in the skin and subcutaneous structures without any significant involvement of breast tissue. Healing occurred without incident, and there has been no recurrent infection.

CASE 2. Mrs. L. P., a 39 year old female, was initially seen in April 1953, in the first trimester of her fourth pregnancy, complaining of bilateral chronic breast abscesses. The first inflammatory episode involving the breasts had occurred 2 years previously during her third pregnancy. Incision and drainage of a breast abscess on the left were carried out at that time. Two weeks following delivery, she developed a periareolar abscess involving the right breast, and this required surgical drainage. These abscesses had continued to drain on a chronic basis with recurrent episodes of tenderness and pain since that time. The patient stated that she had always had inverted nipples.

Examination revealed bilateral inversion of the nipples with associated chronic periareolar abscesses. A sinus tract connecting the chronic abscess cavity and the depths of the inverted nipple was demonstrable bilaterally. Excision of the sinus tracts combined with correction of the inversion of the nipples was carried out in April 1953. The wounds healed without incident and the patient had no difficulty throughout her pregnancy or postpartum period. There has been no recurrence of infection since operation. Pathologic examination of the involved breast tissue revealed chronic inflammatory changes involving the skin and subcutaneous tissues with no evidence of infection of breast tissue.

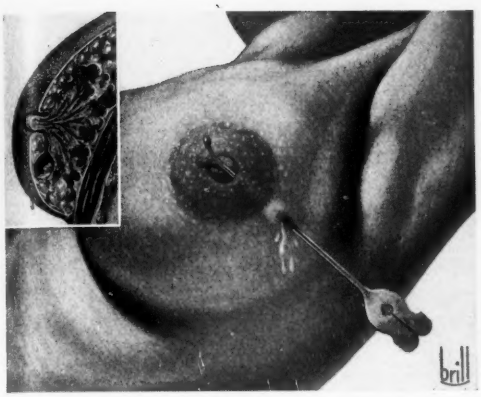

FIG. 4.

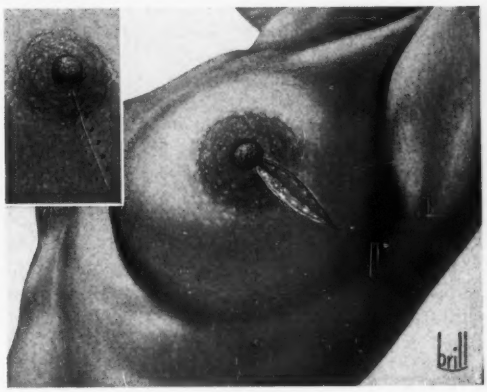

FIG. 5.

FIG. 4. Diagrammatic representation of the pathogenesis of the chronic periareolar abscess. Cellulitis beginning in the "groove" of the inverted nipple secondarily involving the subareolar and periareolar regions with abscess formation.

FIG. 5. Diagrammatic representation of the surgical treatment which consists of an elliptical excision of the sinus tract carried through the areola into the base of the nipple. Closure, with or without drainage, with vertical mattress sutures of alloy-steel wire corrects the inversion.

CASE 3. Mrs. C. B., a 37 year old female, was first seen in June 1954, with the chief complaint of a chronic abscess of the right breast. This abscess had initially occurred 4 years previously, and at that time the first surgical drainage was carried out. Since then there were 4 surgical drainages required, and in each instance these procedures were followed by recurrence of the infection with constant purulent drainage. The patient stated that she had always had bilateral inversion of the nipples.

Examination revealed bilateral inverted nipples with a chronic periareolar abscess on the right. A sinus tract connection could be demonstrated between the abscess cavity and the depths of the inverted nipple. Excision of the sinus tract with correction of the inversion was carried out in June 1954. The pathologic report indicated chronic inflammatory changes in skin and subcutaneous tissues and evidence of significant infection in a single large duct. The patient has had no recurrence of infection since operation.

CASE 4. Mrs. D. N., a 29 year old female, was seen in August 1954, with chief complaints of bilateral inversion of the nipples and a chronic abscess of the left breast. The patient had had her original inflammatory episode involving the left breast approximately 2 years previously, and incision and drainage had been carried out on two separate occasions. In each instance there had been a recurrence of the abscess.

Examination revealed bilateral inversion of the nipples with a chronic periareolar abscess on the left. Initially, it was not possible to demonstrate the sinus tract connecting the abscess cavity with the depths of the inverted nipple due to local pain. Under anesthesia, however, this connection was readily demonstrable, and excision of the sinus tract and correction of the inversion of the nipple were carried out in August 1954. No histologic examination of the removed tissue was carried out. Healing occurred without incident and there has been no recurrence of infection since operation.

CASE 5. Mrs. T. T., a 48 year old Chinese female, was seen in September 1954, with a history of chronic recurrent abscess of the right breast for the past 20 years. There had been multiple incisions and drainages carried out over this period of time, and in each instance recurrence of the infection had occurred. The patient stated that she had always had inverted nipples.

Examination revealed bilateral inverted nipples with a chronic abscess of the left breast. One was able to demonstrate without difficulty the sinus connecting the breast abscess with the depths of the inverted nipple. Excision of the sinus tract and correction of the inversion of the nipple were carried out in November 1954, and the patient has had no evidence of recurrent infection since operation. Pathologic examination of the involved tissue revealed chronic inflammatory changes in skin and subcutaneous tissue without any histologic evidence of infection in the breast tissue.

CASE 6. Mrs. D. G. was first seen in April 1952, with a history of recurrent abscess of the right breast. She stated that her initial episode of infection had occurred in 1942. Over this 10 year period there had been multiple episodes of recurrent infection requiring incision and drainage, and she had had extensive treatment with antibiotics. Wide excision of the

abscess had been carried out in 1953 but this was followed by prompt recurrence of the infection. The patient said that she had always had inverted nipples.

Examination revealed bilateral inverted nipples with a chronic abscess in the right periareolar region. A sinus tract connecting the abscess cavity with the depths of the inversion of the nipple could be readily demonstrated. Excision of the sinus tract and correction of the inversion were carried out in February 1955. The pathologic examination showed inflammatory changes in the skin and subcutaneous tissue without evidence of infection in the breast tissue. The patient has had no recurrence of infection since operation.

SUMMARY

During the past 2½ years we have observed 6 patients with chronic periareolar breast abscesses. All of these patients had a history of multiple recurrence of infection despite various types of surgical treatment. All had associated inversion of the nipples. The chronic abscess cavity was found to connect by a sinus tract to the "groove" of the inversion of the nipple. Excision of the sinus tract and correction of the inverted nipple have resulted in a satisfactory healing without recurrence of the infection in each of the 6 cases for periods of time varying from 8 to 30 months.

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PERIPHERAL ARTERY REPLACEMENT WITH CHEMICALLY TREATED NYLON TUBES

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DESPITE THE SUCCESS of preserved human arteries as vascular grafts in the past few years, certain factors have led to a search for other methods of replacement of diseased or damaged vessels. Human vessels are difficult to procure in adequate numbers, costly and time-consuming to preserve, and occasionally develop late complication of rupture or calcification.

Voorhees and co-workers demonstrated the ability of tailored tubes of nonreactive fabrics such as vinyon N to act as satisfactory blood conduits in animals and man. Other fabrics such as nylon, polyester, and acrylic fibers have been found to be equally satisfactory once they have been implanted in the vascular tree. The difficulty with most tailored tubes lies in the implantation; some fabrics are too loosely woven making hemorrhage a serious problem after release of clamps; the tailoring seams and cuffs make suturing somewhat difficult, and all fabrics tend to kink or wrinkle if the graft crosses a flexion area.

It has seemed that further simplification and improvement would be necessary before fabric tubes could safely and easily be used by many different surgeons without considerable practice in tailoring fabric grafts. A prefabricated tube has therefore been sought that could be made in various sizes, could be easily sutured, and could be made wrinkle or kink-proof on flexion.

In a previous report (1), the evolution of chemically treated flexible nylon tubes was described. These braided tubes of 210 denier nylon yarn are treated with a formic acid dip which swells and partially dissolves the outer layer of each fiber, and allows each fiber to stick to those adjacent to it, thus producing a tube that can be cut at any level at the operating table and can hold arterial sutures without fraying. An additional benefit derived from this treatment is reduction of pore size so that temporary bleeding through the cloth is much reduced. To reduce blood loss through the mesh further, an ether soluble silicone dip has been used since our earliest experience. Thus a porous tube is produced which maintains a cylindrical shape, repels water, and can easily be cut and sutured. The chief remaining difficulty, kinking on flexion, has been overcome by "crimping" the tube. This is done by pushing the two ends together on a glass mandrel after the formic acid treatment, but before the heat setting (140 degrees C.). This circular crimp allows 180 degrees flexion without kinking or obstruction. A number of animal experiments in which the crimped tubes were inserted in the abdominal aorta resulted in a low incidence of thrombosis despite the irregularity on the inside due to the crimps. Tubes as small as 6 millimeters in inside diameter were uniformly successful. Of 10 dogs living from this group of experiments for 9 to 12 months, there have been no cases of late thrombosis of the graft.

A single case was described in the first report of replacement of the common femoral artery by a crimped tube 2 inches (5 cm.) long. It is the purpose of this paper to describe the early results in a later series of 13 additional cases, with modifications in technique that have proved advantageous.

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This project was supported by Grant H-1987 from the U. S. Public Health Service.

FIG. 1. Possible variations in braided tube grafts.

METHODS

Tubes of three sizes have been used clinically in bridging iliac, femoral, and popliteal artery defects. These have inside diameters of 6/16 inch (9.4 mm.), 5/16 inch (7.7 mm.), and 4/16 inch (6.1 mm.). The originally described concentration of formic acid dip produced tubes that were quite stiff, and slightly difficult to handle because of this rigidity. Various concentrations of formic acid have since been carefully tested. A final concentration of 71.4 ± 0.2 per cent formic acid by volume in distilled water produces a tube that is much softer and easier to handle and suture, yet with enough reduction in porosity to prevent blood loss through the cloth. It is necessary to heat-seal the cut end of this softer tube with an actual cautery to prevent fraying at the time of suture. This is easily done at the operating table by the gentle application of the tip of the warm (but not red hot) cautery to the end of the graft in such a way that the tip is not scorched. The tube end will then firmly hold an arterial suture. The tubes are readily sterilized by autoclaving for 20 minutes, and may be resterilized numerous times without damage.

It should be pointed out emphatically at this point that the chemical (formic acid) and physical (heat) modifications of the nylon tube have not changed it chemically or added any new material that might be harmful. Formic acid is a commonly used solvent for nylon, which is carefully removed by prolonged washing. Sealing the tube end by heat is simply another method of melting the nylon temporarily. The final product in either case is pure nylon. The sealed end is slightly stiff but it can be softened by compression a few times between the fingers. Before insertion the crimped tube is compressed by the fingers over its entire length and stretched by pulling the two ends apart. Thus the tube is softened in its central portion so that it will conform to body contours, but it is not made more porous or more likely to kink.

Several modifications of suture technique have evolved with increasing experience. For end-to-end anastomosis, a simple over-and-over continuous suture interrupted twice is perfectly satisfactory at the proximal end of the graft. In larger vessels this type of anastomosis is safe at the lower junction. A definitely smoother and safer anastomosis is produced by pulling the distal host artery up over the lower end of the graft with 3 or 4 interrupted sutures as shown in Figure 2. This maneuver holds the vessel lumen open, and the junction is made blood-tight by a single row of continuous suture or further interrupted sutures. This type of distal anastomosis is particularly advantageous in small vessels.

As has been recently pointed out by Linton and Kunlin, segmental arterial obstructions in the leg can be satisfactorily by-passed without damage to valuable collaterals if a graft can be sutured to the side of the patent vessels above and below the obstructed region. The flexible crimped tubing has proved quite satisfactory for making such by-pass grafts. As shown in Figure 3, small incisions are made over the upper and lower patent arteries and the appropriate sized nylon tube is pulled subcutaneously or subfascially between these two incisions. The cut end of the braided tube is beveled at a 45 degree angle with scissors, then heat-sealed with the cautery. The tube is sutured to a longitudinal incision made in the host vessel. Again the proximal anastomosis is accomplished by a continuous over-and-over stitch of No.

5-0 arterial silk, while the distal end of the graft is made to project slightly inside the longitudinal incision which is accomplished as before by several interrupted sutures as shown in Figure 3, followed by a continuous stitch all around. It is important to introduce the arterial needle from inside out in the sclerotic vessel to avoid separation of intima from media and precipitating intimal dissection when blood flow is resumed. This use of a longitudinal incision for the anastomosis makes it possible to use a graft slightly larger than the patient's vessel, so that a more than adequate blood supply to the distal extremity results.

The use of heat-sealed tube ends and more careful suturing has eliminated the need for reinforcing cuffs around the anastomosis as previously advocated (1). The proper length of tubing is that length which bridges the defect with very slight tension on the tubing.

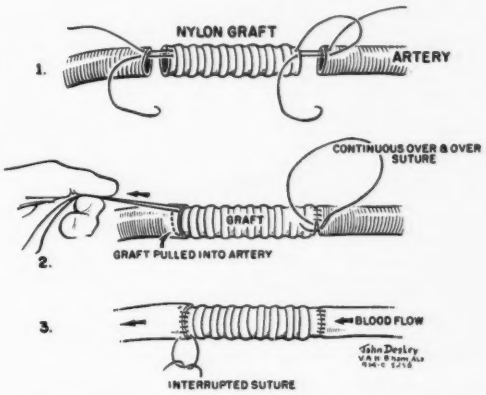

FIG. 2. End-to-end technique, showing the everting stitch at the lower anastomosis which pulls the distal vessel up around the graft.

CLINICAL EXPERIENCE

A total of 14 patients have received 15 nylon grafts in peripheral vessels. Early in our clinical efforts, it was thought that the irregular crimps on the inside would offer serious resistance to blood flow in long grafts, increasing the likelihood of thrombosis; therefore, a number of cylindrical tubes without or with minimal crimps were used. In 1 patient a 15 centimeter straight graft was sutured end-to-end into an arterial defect in the midthigh from excision of an obstructed superficial femoral artery. Peripheral pulses never returned. In 4 other patients long straight grafts with short crimped segments on each end were used as by-pass grafts, around obstructions from 10 to 33 centimeters in the superficial femoral artery. These tubes were sutured to the side of the common femoral above, and to the side of the superficial femoral or popliteal below the obstruction. One graft functioned well for 3 days before pulses disappeared; 2 functioned satisfactorily for 2 weeks at which time thrombosis occurred. One was an immediate failure because of insufficient runoff down the obstructed popliteal branches.

Although all 5 of these grafts containing stiff straight segments were failures, two valuable lessons were learned. Re-exploration of one of these grafts with a long straight central segment convinced us that it is important for a graft to be able to lengthen and shorten upon hip and knee flexion to prevent obstruction by angulation of the junction of the artery with the graft. Secondly, a stiff straight graft, even in an area where

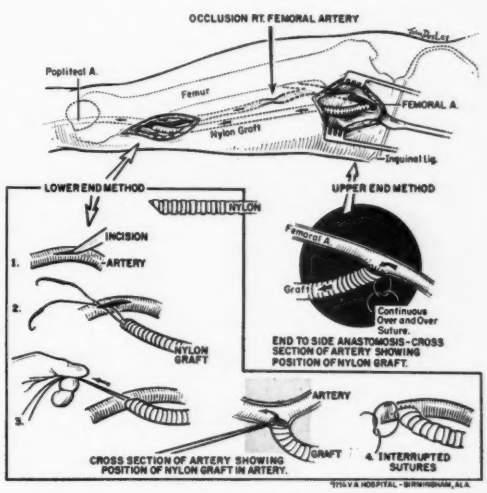

FIG. 3. By-pass graft technique showing suture methods used at upper and lower ends.

flexion does not occur, such as midthigh, cannot readily adapt to bodily contours and may assume an unfavorable angle with relation to the host artery. This observation was made at the time of operation in the first case mentioned, and efforts to align this straight tube with the femoral artery by appropriate sutures in the overlying muscle were unsuccessful.

Our original aim in producing a tube with this considerable degree of stiffness was to allow the tube to hold sutures at any level at which it was cut. Since experimental studies have convinced us that the technique of heat-sealing the cut end of a softer tube will give an even more secure purchase for the arterial stitch, this degree of stiffness is no longer needed. By varying the concentration of formic acid solution, a much more pliable, flexible, and stretchable tube has been developed as previously mentioned, which still has enough resiliency to maintain its nonkinking quality and small enough pores to prevent hemorrhage. Our unfortunate experience with straight segments has led to their abandonment and to the exclusive use of completely crimped tubes in peripheral vessel replacement, whether in a flexion area or not. The following case reports detail our results in the first 10 patients receiving crimped tube grafts.

CASE REPORTS

CASE 1. B. L. (previously reported), was a 58 year old man with cardiac decompensation from valvular disease and from an arteriovenous fistula of the right superficial femoral artery and vein. In the course of repair of the fistula a rubber covered clamp eroded through a sclerotic plaque in the common femoral artery, resulting in a 5 centimeter segment of damaged artery. This gap was bridged by a 5 centimeter crimped tube of ¼ inch diameter without silicone. Pedal pulses were restored immediately and remained strong even with acute hip flexion for 4 months. At this time the patient died suddenly at home after experiencing a sudden precordial chest pain. No autopsy was obtained. A presumptive diagnosis of coronary thrombosis was made.

CASE 2. McD. L., a 27 year old male, was shot in the right groin by a .38 caliber pistol. Lacerated artery and vein were clamped in the emergency room and blood pressure was restored by 7 transfusions. At surgery, inspection revealed that the superficial femoral vein was torn, the artery was lacerated and contused over a 2 centimeter distance, beginning immediately below the femoral bifurcation. In keeping with the experience reported by Jahnke and Seeley from Korea the artery was resected 1 centimeter beyond the area of obvious gross contusion and the 4.5 centimeter defect bridged by a ¼ inch diameter crimped graft (treated with silicone) sutured end-to-end. Each anastomosis was wrapped with nylon tape and there was almost no bleeding after release of clamps. The femoral vein was ligated. Pedal pulses were restored and have remained strong for 9 months at the time this is written. Acute flexion of the thigh causes no diminution of pedal pulses.

This high velocity missile injury resembles war time vascular damage, and successful restoration of flow has encouraged us to hope that this simple tube may be useful in times of conflict.

CASE 3. J. S., an 81 year old man, was admitted to the hospital with a gangrenous right foot and leg from sudden obstruction in a popliteal aneurysm. Examination revealed a large popliteal aneurysm in the left leg as well, but with strong pedal pulses. A supercondylar amputation was performed on the right. Seven days later the left popliteal aneurysm was excised and a 6 inch (15 cm.) long, crimped nylon tube of 5/16 inch (7.7 mm.) inside diameter was sutured end-to-end into the defect. This graft has remained patent for 8 months and pulses remain strong despite flexion of the knee. Figure 4 demonstrates an arteriogram taken 2 weeks after insertion showing patency with partial knee flexion.

CASE 4. B. J., a 19 year old boy, was severely injured when he was thrown from a truck in which he was riding. He sustained a penetrating injury of his peritoneum and right posterior thigh and hip by striking a sharp wooden post. His rectum was lacerated, the urethra was disrupted, the right hip and pelvis were shattered, and the right iliac artery and vein were severely contused and thrombosed. The right leg was cold, paralyzed, and tensely swollen upon admission. In the operating room, a loop sigmoid colostomy and a suprapubic cystostomy were performed. The torn right iliac vein was ligated and a 10 inch (22 cm.) length of badly contused and thrombosed external iliac and common femoral artery was excised. Good retrograde bleeding was obtained from the superficial femoral artery. A 5/16 inch diameter crimped nylon graft was sutured end-to-end into this 10 inch defect. There was little bleeding when the clamps were released but the patient's blood pressure which had been maintained at 100 systolic until that time with 3 blood transfusions, suddenly fell to 50–60 systolic and the leg became

more tensely swollen. Despite multiple transfusions and constant norepinephrine drip, this patient's blood pressure could not be maintained and he died 10 hours after the operation was completed. Peripheral pulses never returned in this leg but pulsation could be felt over the graft in the right groin until the time of death.

CASE 5. A. B., a 50 year old bricklayer, had for 6 months suffered limitation of walking distance to one-half block from intermittent claudication in the left calf and posterior thigh muscles. A weak external iliac artery pulsation could be felt above Poupart's ligament on the left, with no pulses below. The left foot was cool but without trophic changes or color changes on dependency. The right femoral pulse was strong, none were palpable below, and there were no symptoms in this leg. A lumbar aortogram revealed a complete obstruction in the external iliac and common femoral artery on the left, approximately 10 centimeters in length, with a patent superficial femoral artery. Through two incisions, one extraperitoneal in the left lower abdomen and a second in the left upper thigh, a 5/16 inch crimped nylon graft 15 centimeters long was sutured to the side of the iliac above and to the superficial femoral below the obstruction as a by-pass graft. Pedal pulses were present the following day and have remained strong for the ensuing 8 months. He has returned to bricklaying with no further claudication. Acute flexion of the left hip does not diminish the pulses in the left foot.

CASE 6. J. T., a 40 year old man, had suffered progressive claudication in the right calf for 9 months. Femoral arteriogram demonstrated a long segmental occlusion from common femoral to popliteal artery. A 5/16 inch diameter crimped nylon graft 39 centimeters in length was sutured to the side of the common femoral above and popliteal below. A much more dilute solution of formic acid treatment had been used on this graft to make it more flexible, and make a tube that would shorten and lengthen with flexion and extension of the leg. After the clamps were released, severe hemorrhage occurred through the mesh, making reapplication of the clamps necessary. By the time adequate clotting had occurred in the mesh to prevent blood loss, it was found that the lumen of the graft was obstructed by thrombosis. Several incisions were made in the graft and the clot was milked out, finally restoring a pulse through the tube. After operation, distal pulses never returned and it is believed that the graft immediately thrombosed.

This single failure demonstrates the hazard of a porous mesh, and the danger from reapplying clamps after the graft is filled with blood. Needless to say, tubes with this degree of porosity have not been used again and all other grafts here reported have had a stronger concentration of formic acid dip so that hemorrhage has not been a problem.

FIG. 4. Postoperative arteriogram 2 weeks after insertion of a 6 inch long, crimped nylon tube in the popliteal artery to replace an aneurysm (Case 3). Note the disappearance of the internal irregularities and the ability of the graft to flex without kinking.

CASE 7. F. A., a 58 year old man, entered the hospital with gangrene of the right great toe and severe ischemia and constant pain in the adjacent toes. Neither femoral pulse was palpable, but there were no symptoms in the left leg. A lumbar aortogram (Fig. 5) demonstrated a complete occlusion in the right iliac and common femoral artery approximately 15 centimeters in length with a patent superficial femoral and popliteal artery to the knee. A 20 centimeter crimped nylon graft (6/16 inch diameter) was sutured to the side of the common iliac above and the superficial femoral below the block as shown superimposed on the aortogram. The popliteal pulse returned, the right foot became warm, ischemic pain disappeared. A transmetatarsal amputation was performed and healed rapidly. This graft has functioned well for 4 months.

CASE 8. L. L., a 28 year old housewife, was injured by a pistol wound of the right groin several hours before admission to the hospital and massive hemorrhage resulted. Immediate exploration revealed a through-and-through wound of the common femoral artery with contusion for about 1 centimeter proximal and distal to the area of injury. Four centimeters of artery were resected back beyond the area of contusion and a 4 centimeter crimped nylon graft was sutured end-to-end into this defect. This graft was 5/16 inch in diameter and was anastomosed to the common femoral immediately above the common femoral bifurcation in an effort to preserve the deep femoral vessel. Pulses were immediately restored and she has continued to do very well for a period of 2 months.

FIG. 5. A 20 centimeter, crimped nylon graft superimposed on the aortogram to demonstrate the by-pass technique used successfully in Case 7.

CASE 9. J. R. K., a 52 year old man, was shot in the upper third of the thigh 1 week before entry into the hospital. He was found to have a large pulsating subfascial hematoma which on incision was found to connect directly with the superficial femoral artery. Tourniquet control in the groin prevented any further blood loss. The artery was dissected and found to contain a longitudinal laceration about 1½ centimeters in length communicating with the hematoma. The artery was very friable and in dissecting out this lacerated area some damage was done to the artery proximal to the injury and it was necessary to resect a 7 centimeter length of artery. A crimped nylon graft 7 centimeters long and 5/16 inch inside diameter was sutured end-to-end into this defect and pedal pulses were immediately restored. This defect lay in the upper third of the superficial femoral artery. The patient's postoperative course was uneventful and good circulation has been maintained for 2 months.

CASE 10. W. D. O., a 60 year old retired civil service worker, a mild diabetic, had suffered progressive claudication in the left calf muscles for 16 months until his walking distance was shortened to ½ block. Both femoral pulses were strong, and all were absent below in the left leg but present in the right leg to the foot. There was no dependent rubor and no gangrene. Left femoral arteriogram revealed a very long superficial femoral artery obstruction in this tall thin man, with good filling in the popliteal and its branches. A 15½ inch (34 cm.) long straight graft with 2 inch crimped segments on each end was used to by-pass this obstruction, suturing the graft to the side of the common femoral above and the popliteal below. The foot immediately grew warm, pedal pulses returned and were present until the fourteenth day—the first day he became ambulatory—then disappeared, and the foot became cool again. Before this happened, the observation was made that the pedal pulses could be made to disappear by flexing the hip and knee. This graft was one of the failures of straight stiff grafts reported before. The patient was subjected to bilateral lumbar sympathectomy and discharged, to discover that his claudication was as severe as ever. He was, therefore, readmitted 5 months later and a 17 inch (37 cm.) completely crimped nylon graft, 5/16 inch in diameter, was sutured to the side of the common femoral above the previous graft and to the side of the popliteal below the former implant, which was not disturbed. The graft was pulled subcutaneously through the thigh between the upper and lower incision. Blood loss was no problem, and peripheral pulses again returned and have remained for 2 months with disappearance of his claudication.

The early results in 10 consecutive patients with artery replacement by crimped tubes have been very encouraging. A much longer period of observation will be necessary to determine how long these grafts will remain patent in the human and whether

degenerative changes will occur. Grafts removed from animals sacrificed after 1 year have shown a very thin smooth inner lining without the slightest evidence of calcium deposition.

The very high incidence of thrombosis in stiff straight grafts in peripheral artery replacements has caused this type to be completely abandoned. It is possible that larger caliber straight tubes may be satisfactory in the human abdominal and thoracic aorta where lengthening and shortening are not necessary, but this remains to be tested. Straight grafts function quite well in the abdominal and thoracic aorta of the dog.

SUMMARY

Flexible braided nylon tubes, treated with acid, have been developed and have the following characteristics:

1. Grafts of various lengths and diameters can be made readily available.

2. These tubes may be sterilized by autoclaving.

3. They are very easily handled and sutured.

4. The incidence of thrombosis is low, even in small vessels.

5. Little blood loss occurs through the tube after implantation.

6. They are flexible to 180 degrees without obstruction; therefore, they can be used (a) in flexion areas, groin, axilla, popliteal space; and (b) as a by-pass graft around an obstruction.

Ten cases of peripheral vessel replacement with crimped tubes are reported with success in 9. Difficulties with straight grafts have caused their abandonment.

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IMMUNOLOGIC STUDIES IN RENAL HOMOTRANSPLANTATION

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THE TECHNICAL ABILITY to transplant organs and tissues has far exceeded our understanding of the mechanisms involved. It is possible to transplant lung, heart, kidney, spleen, adrenal, ovary, and even liver from one animal to another. However, except for a few isolated situations, all such homotransplants fail to survive and function for any appreciable length of time. The mechanism by which homografts are destroyed is under investigation in many centers at the present time.

It has become gradually accepted in the past 10 years that homograft rejection is based on immune mechanisms. Perhaps the most convincing evidence on this point comes from Medawar's demonstration in rabbits (23) that a second skin graft from the same donor to the same host has a much shorter survival period than the primary graft. Many other workers have confirmed this so-called "second-set" phenomenon, and Dempster (8) has demonstrated that a previous skin graft will make a later kidney transplant behave as a second-set homograft. It is believed that antibodies are produced against antigenic material in the graft, and that a second graft from the same donor is destroyed by such antibodies. Most antibodies are found in the gamma globulin fraction of the plasma. A successful homograft of skin in a child with agammaglobulinemia has recently been reported by Good and Varco. This has been interpreted as meaning that antibody production is necessary for homograft rejection, and the patient with agammaglobulinemia is unable to produce antibodies to the transplant. Michon and co-workers observed a steady rise of gamma globulin in the blood of a 16 year old boy with a kidney homotransplant which functioned for 21 days. It was postulated that this increase in gamma globulin represented antibody to the transplanted kidney.

Cannon and Longmire found that skin homografts would often survive in the newly hatched chick, and that a progressively smaller incidence of survivals was obtained as grafts were placed in older chicks. Billingham, Brent, and Medawar (3) found that the intrauterine injection of mouse fetuses with whole blood or skin extracts resulted in a state of tolerance in the mature fetuses to future skin homografts from the donor of the blood or skin. Viable homografts on such intrauterine injected animals may be destroyed by grafting lymph node tissue from normal animals previously grafted from the same donor (4). Killed lymph node tissue was ineffective, indicating that viable lymphoid tissue produced antibody to the graft.

Hardin and Werder have recently demonstrated that irradiation of the donor and host prior to skin homografting in mice results in over 50 per cent graft survival. The same authors achieved almost 50 per cent survival of skin homografts by injecting skin extracts of the donor into the host prior to transplantation. The irradiation effect is presumably based on depression of the antibody-forming mechanisms, and it is believed that pretreatment with skin extracts produces a condition of "immunoparalysis" as described by Felton. According to Felton, mice injected intravenously with large quan-

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tities of a pneumococcus polysaccharide, were thereafter unable to manufacture antibodies to the polysaccharide. Billingham and co-workers (5) have demonstrated that cortisone will prolong the survival time of skin homografts in rabbits, probably as a result of depression of the antibody-forming mechanism.

All of the previously mentioned findings appear to be best explained on an immunologic basis. However, the major drawback to acceptance of an immune basis for homograft rejection has been the failure to demonstrate antibody to the homograft by in vitro techniques. Simonsen (28), using complement fixation, did not succeed in demonstrating antibodies against renal tissue from donor dogs, in recipient serum. Favour and co-workers found little change in serum complement during the course of renal homograft destruction in dogs. Amos and co-workers have recently demonstrated that skin homograft recipients produce agglutinins to both red and white blood cells of the donor. However, specific antibodies against antigenic material in the grafted skin have not been demonstrated in vitro thus far, to the best of our knowledge.

The experiments in this study have been devised to allow an in vivo assessment of antigenicity and antibody production. The development of a simple, safe, and effective cross circulation technique (10, 11) has made it possible to intermingle the blood streams of dogs over long periods of time. Part I of this study is a control series of 60 primary kidney transplants. Part II consists of a series of renal homotransplant pairs in which cross circulation or plasma or splenic extract injections were performed at different periods after transplantation. Movement of antibody from host to donor animal was looked for by means of serial biopsies of the remaining donor kidney after cross circulation. Part III is an evaluation of the effect of a period of cross circulation between donor and recipient prior to primary renal homotransplantation or simultaneously with it. If previous cross circulations were to result in "immunization," then the primary homotransplant should behave as a second-set graft, with accelerated destruction and microscopic changes characteristic of secondary transplants.

MATERIALS AND METHODS

Healthy adult mongrel male dogs ranging in weight from 12 to 30 kilograms were used in the study. All operations were performed under sterile conditions and intravenous sodium pentobarbital was used for anesthesia. Animals of approximately the same size but dissimilar body characteristics were chosen for each transplantation experiment. The kidneys of both animals were exposed through a right subcostal incision and the ureter of the donor animal was cannulated with a No. 190 polyethylene tubing (Clay-Adams, animal tested). The right kidney was chosen for transplantation experiments in the dog because of the high incidence of double renal artery on the left side in this animal. Bulldog clamps were placed low on the right renal artery and vein of the recipient animal, and the kidney was removed.

The donor kidney was then removed and the renal vessels anastomosed to those of the host with a continuous suture of No. 5–0 silk. Two stay sutures were used on the renal artery anastomosis, and 3 on the vein. After completion of the two anastomoses, the bulldog clamps were removed and blood flow was resumed through the kidney. The period of anoxia was 20 to 25 minutes. Depending somewhat on the state of hydration of the animal, clear urine usually started dripping from the ureter catheter of the transplant within a few minutes after the procedure. All recipient animals were given 500 cubic centimeters of normal saline during or at the end of the transplantation, and this invariably resulted in an increase in urine flow from the transplant. Inasmuch as the ureteral catheterization often results in mild bleeding and a tendency to form clots in the polyethylene catheter, the increased urine flow which results from administration of intravenous saline is considered important

to the procedure. The polyethylene catheter in the ureter was brought out through the anterior abdominal wall of the recipient animal and connected to a plastic bag pinned to the inside of a canvas jacket placed on the animal. Daily collections of urine were made and aliquots saved for determinations of specific gravity, albumin, urea, nitrogen, creatinine, nitrogen, and microscopic inspection.

The experiments of Part II are divided into three sections. All recipient animals were followed until there was cessation of transplant function, as evidenced by a daily urine volume of less than 50 cubic centimeters or the presence of blood in the urine. In Section 1 of these experiments, when the transplant ceased functioning the transplant dog was exsanguinated into a sterile citrate bottle. At the same time the kidney transplant was removed, and sections were placed in 10 per cent formalin for microscopic study. The blood was then centrifuged at 3,000 revolutions per minute for one-half hour, and the plasma was drawn off into a plastic bag.

The donor dog was then operated upon through a left subcostal incision, and the aorta and left renal artery were mobilized. A Pott's clamp was then placed on the aorta below the left renal artery, a needle leading from the plastic bag containing the transplant's plasma was inserted into the aorta opposite the left renal artery, and the plasma was infused into the aorta and carried into the left renal artery by the aterial pulse. Plasma injection proceeded uneventfully, and at its completion the Pott's clamp was removed and the needle withdrawn from the aorta. Prior to the plasma injection a biopsy of the donor's left kidney was taken and biopsies were repeated again at intervals after the dog had recovered from the injection. The biopsies were placed in 10 per cent formalin for microscopic study at a later date.

In the second section of these experiments, splenectomy was performed in the recipient animal at the time of cessation of function of the transplant. An extract of the spleen was made by placing it in a blender turned on for 3 minutes and off for 2 minutes for a total time of one-half hour. The supernatant from this homogenate was centrifuged at 3,000 revolutions per minute for 15 minutes. The supernatant from this centrifugation, a brownish, translucent fluid containing moderate numbers of tissue cells was injected into the left renal artery of the remaining kidney of the donor by the same method used in the plasma experiments. Biopsies were performed of the remaining donor kidney before splenic extract injection and at intervals after recovery of the animal.

Section 3 experiments of Part II utilized a cross circulation technique performed intermittently either during the time of transplant function or following removal of a necrotic transplant. A carotid artery of each animal was connected to an external jugular vein of its partner by polyethylene tubing (No. 350, Clay-Adams, animal tested), and the animals were heparinized at a dosage of 2 milligrams per kilogram, repeated every 6 hours. Artery and vein were recannulated for each cross circulation procedure. Blood flows between the cross circulating animals were determined by means of a rotameter. Biopsy of the remaining donor kidney was performed before cross circulation procedures and at intervals after them. A series of control experiments in animals without kidney transplants were carried out, in which a period of cross circulation was followed by a kidney biopsy a week later and the cycle repeated.

Part III was divided into three sections. In one, animals which had been previously transfused with blood or plasma from another animal received 1 week later a kidney transplant from the donor of the transfused blood or plasma. In some instances reciprocal transfusions of 300 cubic centimeters of whole blood were given between future donor and future host, and in other instances 300 cubic centimeters of whole blood were simply transfused from donor into host. In some instances, 300 cubic centimeters of plasma were transfused from future donor into future

host, with whole blood replacement into the donor from another dog. Kidney homotransplantations were performed in these previously transfused animals according to the technique previously described.

Experiments in Section 2 of this group consisted of transplantations in animals that had previously been subjected to cross circulation. The times of cross circulation and the interval between cross circulation and homotransplantation were varied in this series. Function of the transplant was followed as described, and it was removed when function ceased.

In Section 3, kidney homotransplantation was performed and at the same time the animals were put in cross circulation. In order to allow continuation of cross circulation after recovery from anesthesia, the necks of the 2 dogs were joined together with plaster as described elsewhere (12). The cross circulation polyethylene cannulas were exteriorized so that blood flow could be determined and small polyethylene catheters were placed in external leg veins to allow intermittent injections of heparin. A dosage of 2 milligrams per kilogram every 6 hours was found necessary to prevent thrombosis in the cannula. In most instances, after recovery from anesthesia, the animals could ambulate despite the presence of the plaster collar and were usually able to eat and drink. In 1 experiment, cross circulation and simultaneous transplantation were performed in previously cross circulated animals, and in 3 the dual procedure was done in animals not previously operated upon.

RESULTS

Part I

Sixty primary kidney homotransplants form the background material for this study. Fifty-six of these 60 primary homotransplants secreted clear urine after transplantation, 3 were technical failures, and 1 failed to secrete urine despite apparently adequate vascular anastomoses. The average secretory time for the kidneys that did function was 5.9 days. Increasing albuminuria usually prefaced cessation of transplant function. The usual gross picture of the enlarged soft transplant removed when function ceased included a greatly widened cortex on cut surface covered with a diffuse, white splotching, often a dark zone between the cortex and medulla, and usually a normal appearing medulla. Microscopically, the primary homotransplant is characterized by large collections of interstitial plasma and mononuclear cells, necrotizing arteritis with obstruction, interstitial hemorrhage, and usually relatively normal glomeruli. No primary transplant in this series functioned for less than 3 days and 1 secreted over 50 cubic centimeters of clear urine for 14 days. The gross and microscopic variation in primary homotransplants has been emphasized in a previous communication (20).

Part II, Sections 1 and 2

Effect of recipient plasma and splenic extract injected into renal artery of remaining kidney of the donor. In 3 experiments, 500 cubic centimeters of plasma from the transplant dog were injected into the renal artery of the remaining donor kidney. Preinjection biopsies of the kidney were normal in all 3 experiments. Biopsies of the remaining donor kidney performed at 2, 5, and 8 days after plasma injection revealed that the kidney was not affected by the injection. In 1 of the experiments an occasional small focal collection of mononuclear cells was present in all the kidney biopsies, including the one taken before plasma injection. The renal transplant had run a typical course in the 3 recipient dogs from which plasma was obtained. Urine was secreted in good quantities for several days, and the homotransplants showed characteristic gross and microscopic changes.

In 2 pairs of animals, splenic extracts made from the recipient dog were injected into the renal artery of the remaining donor kidney. Biopsies of the remaining donor kidney taken before the injection were normal, as were biopsies performed 3 and 7 days after spleen injection. Spleen extracts were made from animals whose kidney transplants functioned

TABLE I.—SUMMARY OF INTERMITTENT CROSS CIRCULATION EXPERIMENTS PERFORMED BETWEEN DONOR AND HOST AFTER PRIMARY HOMOTRANSPLANTATION

Exper. No.	*Function of transplant until removal*	*Sequence of cross circulation procedures*	*Times of donor kidney biopsy and pathologic examination*
1	Five days of clear urine of volume 60 to 620 c.c. on 6th day 22 c.c. bloody urine. Sixth day typical primary transplant removed*	1st, 2nd, 3rd, 4th, 6th postoperative days—cross circulated for 15 to 30 mins. at flow of from 400 to 500 c.c./min.	7th day—donor kidney grossly and microscopically normal†‡
2	Five days of clear urine of volume 200 to 400 c.c. On 6th day urine became bloody and typical primary transplant removed	3rd day—cross circulated 6 hr. at 500 c.c./min. 6th day—cross circulated 6 hr. at 480 c.c./min.	6th day—grossly and microscopically normal. 8th day—grossly and microscopically normal
3	Seven days clear urine of volume 50 to 230 c.c. 8th day no urine and primary transplant with renal vein thrombosis removed	5th day—cross circulated for 10 hr. at 520 c.c./min.	8th day—some interstitial hemorrhage in kidney but otherwise normal. Donor dog had distemper
4	Three days clear urine of volume 60 to 120 c.c. 4th day bloody urine and typical primary homotransplant removed	4th day—cross circulated 24 hr. at 600 c.c./min.	5th day—grossly and microscopically normal
5	5 days clear urine of volume 50 to 325 c.c. 6th day no urine and typical primary transplant removed	6th day—cross circulated 3 hr. 40 min. at 620 c.c./min. 9th day—cross circulated 3 hr. 30 min. at 350 c.c./min.	6th day—grossly and microscopically normal. 9th day—grossly and microscopically normal
6	4 days clear urine of volume 60 to 250 c.c. 5th day—bloody urine and typical primary transplant removed	5th day—cross circulated 4 hr. at 750 c.c./min. 8th day—cross circulated 4 hr. at 620 c.c./min.	6th, 8th, 9th days—grossly and microscopically normal
7	6 days clear urine of volume 150 to 200 c.c. 7th day bloody urine—typical primary transplant removed	7th day—cross circulated into donor's renal artery 20 min. at 100 c.c./min.	30 days—grossly and microscopically normal
8	8 days clear urine of volume 40 to 620 c.c. 9th day—no urine and typical primary transplant removed	15th day—cross circulated 4 hr. at 450 c.c./min. 43 days—cross circulated 3 hr. at 350 c.c./min.	15th, 24th, 50th days—grossly and microscopically normal
9	9 days urine of volume 50 to 650 c.c. 9th day—removal of typical primary transplant	15th day—cross circulated 3 hr. at 520 c.c./min.	15th, 29th days—grossly and microscopically normal

*Typical primary transplant is one in which there is enlargement of the kidney, round cell infiltration, interstitial hemorrhage, and tubular necrosis.
†Occasionally there are small focal collections of mononuclear cells in kidney biopsies of normal dogs. A small amount of interstitial hemorrhage frequently accompanies the heparinization necessary in the cross circulation procedure.
‡All numbers of days refer to days after transplantation.

for several days and were typical primary homotransplants grossly and microscopically.

Section 3

Effect on remaining donor kidney of cross circulation between donor and recipient after transplantation. Control experiments were performed which indicated that the cross circulation procedure itself did not result in changes in the lungs, spleen, or liver, of either of the cross circulated animals. Kidney biopsies were obtained prior to cross circulation in these controls, and again a week after periods of cross circulation ranging from 2 to 5 hours at a flow of from 200 to 700 cubic centimeters per minute. None of these biopsies revealed any significant change in kidney tissue as a result of the cross circulation procedure.

Table I summarizes results obtained when cross circulation was performed between donor and host either during the period of function of the transplant or after the transplant had ceased functioning and had been removed. In experiment 1, cross circulation was performed for short periods during 5 of the 6 days of function of the transplant. No changes in the remaining kidney of either donor or recipient resulted. In experiments 2, 3, and 4, periods of cross circulation ranging from 6 to 24 hours were performed at a time when the homotransplant reaction was at its peak. Even these prolonged periods of blood stream intermingling between donor and host at the time of transplant rejection did not result in changes in the remaining donor kidney. In experiments 5 to 9, cross circulation was performed after the trans-

TABLE II.—SUMMARY OF TRANSPLANTATION EXPERIMENTS PERFORMED AFTER A PREVIOUS PERIOD OF CROSS CIRCULATION

Exper. No.	*Days between cross circulation and transplantation*	*Length and flow of cross circulation*	*Days of function of transplant**	*Gross features of transplant*	*Microscopic picture of transplant*	
1	8	6 hr., 650 c.c./min.	—1	Slightly enlarged artery and vein open. Good venous flow. Kidney red on cut surface	Hemorrhage 2+ Tubular necrosis 4+ Tubular casts 3+	Interstitial edema 1+ Glomeruli normal endothelial shedding 1+
2	7	600 to 900 600 to 900 c.c./min.	1	Slightly enlarged kidney artery and vein open. Good venous flow. Kidney red on cut surface	Hemorrhage 2+ Tubular necrosis 3+ Tubular casts 3+	Glomeruli normal Blood vessels normal
3	7	5 hr., 600 to 850 c.c./min.	—1	Kidney enlarged. Good venous flow. Kidney red on cut surface	Tubular casts 2+ Tubular necrosis 1 to 2+ Glomeruli and blood vessels normal	
4	5	5 hr., 700 c.c./min.	1	Kidney enlarged. Good venous flow. Kidney red on cut surface	Hemorrhage 3+ Tubular casts 3+ Tubular necrosis 3+ Glomeruli normal	Endothelial shedding 1+
5	4	2 hr., 600 c.c./min.	2	Kidney slightly enlarged. No flow although artery and vein open. Red on cut surface	Hemorrhage 4+ Tubular necrosis 4+ Tubular casts 3+	(Picture of vein thrombosis)
6	7	65 hr., 600 c.c./min.	—1	Kidney slightly enlarged. Good venous flow. Red on cut surface	Hemorrhage 3+ Tubular necrosis 3+ Tubular casts 3+	Endothelial shedding 1+ Glomeruli normal
7	9	3 hr., 620 c.c./min.	4	White splotching of cortex, normal medulla. Good venous flow		
8	5	4 hr., 700 c.c./min.	1	No enlargement of kidney. Decreased venous flow. Dull red on cut surface	Tubular necrosis 4+ Hemorrhage 3+ Tubular casts 2+ Endothelial shedding 2+ Glomeruli normal	
9	11	2 hr., 400 c.c./min.	1	No enlargement. No venous flow. Dull red on cut surface	Infarct	
10	3	3 hr., 250 c.c./min.	1	No enlargement. Greatly decreased venous flow. Dull red on cut surface	Hemorrhage 4+ Tubular necrosis 4+ Endothelial shedding 2+	Glomeruli hypercellular and in many cases fill capsule
11	21	5 hr., 320 c.c./min.	7	Kidney enlarged. Good venous flow. White splotching of cortex	Mononuclear cells 3+ Hemorrhage 2+ Endothelial shedding 2+	Glomeruli Hypercellular and fill capsule
12	14	5 hr., 400 c.c./min.	—1	No enlargement. Good venous flow. Kidney red on cut surface	Hemorrhage 4+ Tubular necrosis 3 to 4+ Mononuclear cells 1 to 2+ Blood vessels and glomeruli normal	
13	12	5 mins., 500 c.c./min.	1	Kidney not enlarged. Decreased venous flow. Kidney red on cut surface	Focal mononuclear cells 1 to 2+ Hemorrhage 2+ Tubular necrosis 1+ Glomeruli and blood vessels normal	
14	18	3 hr., 250 c.c./min.	2	Thrombosis both artery and vein	Infarct	
15	28	2 hr., 600 c.c./min.	1	Kidney not enlarged. Decreased venous flow. Red on cut surface	Hemorrhage 4+ Tubular casts 3+ Glomerular and tubular necrosis 3 to 4+	Blood vessels normal

* day of function implies a urinary output by transplant of over 50 cubic centimeters.

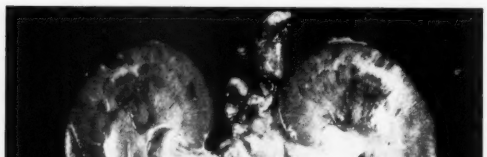

FIG. 1. Primary kidney homotransplant. Note mottled and widened cortex.

plant ceased to function and had been removed. Biopsies of the remaining donor kidney at intervals after this cross circulation procedure again revealed completely normal kidney. It is to be emphasized that all the transplants in this series functioned for several days and were typical grossly and microscopically.

Part III, Section 1

Effect of transfusion from donor to host prior to transplantation. In 4 experiments, a single transfusion of 300 cubic centimeters of blood was given from future donor into future host from 7 to 14 days before transplantation. In 2 of these experiments, the donor transfusion was accompanied by a reciprocal 300 cubic centimeter blood transfusion from the future host back into the future donor. These 4 transplants followed courses indistinguishable from the typical primary transplant,

TABLE III.—RESULTS IN EXPERIMENT ON ANIMALS PREVIOUSLY CROSS CIRCULATED

Day after transplantation	*Urine output*	*Sp. gravity*
1	200	1.032
2	280	1.027
3	220	1.007
Dogs separated from cross circulation		
Biopsy of transplant—normal kidney—		
4	100	1.010
5	160	1.013
6	Blood	
7 Transplant removal	Artery and vein thrombosed, kidney large and red	

Kidney transplantation plus cross circulation in a pair of dogs cross circulated for 68 hours at 240 c.c./min. 10 days before transplantation, in whom cross circulation was again established at the time of renal homotransplantation.

with several days of adequate urine output and extensive round cell infiltration and vascular changes as the outstanding microscopic characteristics upon transplant removal.

In 2 instances, transplantation was performed 1 week after plasma transfusion from donor into host. The transplants functioned for several days and demonstrated the microscopic features of primary homotransplants.

Section 2

Effect of cross circulation before transplantation. Fifteen pairs of animals were cross circulated prior to transplantation. In Table II there is a detailed presentation of these data. It can be seen that 11 of the 15 precross-circulated transplants functioned for 1 day or less. The principal gross feature noted when these transplants were removed was a rather diffuse redness of the cut surface of the kidney as compared to the normal kidney. Microscopically, these precross-circulated transplants were characterized by extensive interstitial hemorrhage, tubular necrosis, and the presence of tubular casts. The glomeruli of most of the transplants were relatively uninvolved. This picture of rapid transplant destruction occurred following periods of cross circulation as short as 5 minutes and as long after the cross circulation procedure as 28 days. It is to be noted that all these transplants were secreting clear urine immediately following the operative procedure and that the vascular anastomoses appeared normal in all respects.

By contrast, in 1 of these experiments the transplant functioned for 7 days and when removed appeared grossly and microscopically like a typical primary transplant. Another transplant in this series functioned for 4 days and appeared grossly like a primary transplant although no microscopic section was available.

Figure 1 illustrates a primary kidney homotransplant removed after 7 days of over 50 cubic centimeters of urine output. In this kidney, as in the primary transplant in Figure 2, there is marked edema and ischemia of the

cortex. The predominant microscopic feature of this cortex is round cell infiltration, with variable edema and necrotizing arteritis. In Figure 3 may be seen the gross features of a secondary kidney homotransplant performed 2 weeks after removal of the primary. The cortex is hemorrhagic microscopically. Figures 4, 5, and 6 are examples of precross-circulated primary homotransplants. All are darker on cut surface than the normal kidney, and microscopically show interstitial hemorrhage, tubular necrosis, and edema.

Section 3

Experiments with transplantation plus cross circulation. In this group of 4 experiments cross circulation was started immediately after kidney transplantation was completed and the animals were immobilized together with a plaster collar. In 1 of these experiments, the animals had been cross circulated for 68 hours at 240 cubic centimeters a minute, 10 days before the transplantation. All of the other 3 transplantations were performed in dogs not previously operated upon. The results in the experiment in which the animals had been previously cross circulated are outlined in Table III. Biopsy of the transplant after 3 days of good urinary output revealed a normal kidney except for the presence of a few focal collections of round cells. Two days after the animals were separated from cross circulation, the transplant ceased functioning and at removal both artery and vein were thrombosed. Technical reasons prevented the successful accomplishment of cross circulation plus transplantation for the whole period of transplant function in the other 3 experiments. Insufficient heparinization resulted in thrombosis of the cross circulation cannulas, on the second day in 1 experiment, the third day in a second, and on the fourth day in a third. In all these experiments the transplant was functioning well and putting out over 100 cubic centimeters of urine a day. All 3 of these transplants appeared grossly normal, although focal round cell collections were present in one minimal and interstitial hemorrhage in another. The transplant that functioned for 4 days before thrombosis of connecting tubings had a small number of tubular casts, some interstitial hemorrhage, and a moderate amount of focal round cell infiltration. In previous experiments utilizing this technique of uncontrolled cross circulation in unanesthetized dogs, it was found that periods of cross circulation up to 87 hours in length did not result in significant changes in organs of cross circulated animals.

FIG. 2. Primary kidney homotransplant.

DISCUSSION

Medawar (26) demonstrated that rabbit skin would grow in serum from another

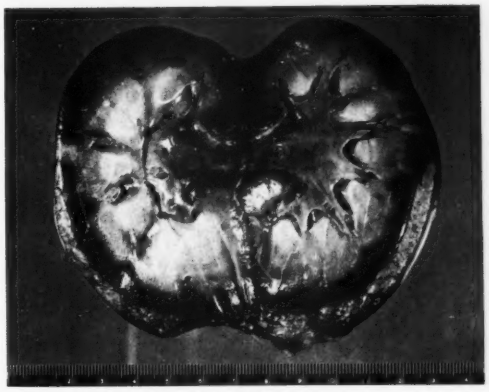

FIG. 3. Secondary kidney homotransplant. This kidney functioned for only 1 day. Cortex is dark red.

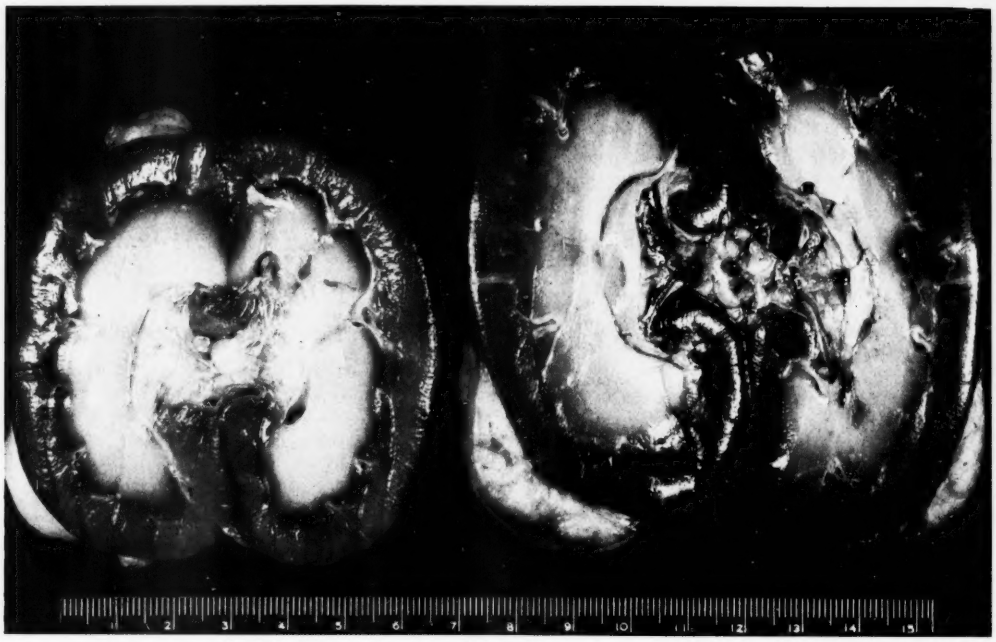

FIG. 4.

FIG. 5.

FIG. 4. Precross-circulated primary kidney homotransplant. Donor and host were cross circulated for 3 hours, 1 week prior to transplantation. The transplant functioned for only 1 day. Normal specimen is shown at the left.

FIG. 5. Precross-circulated primary kidney homotransplant. Donor and host were cross circulated for 5 hours, 1 week prior to transplantation. The transplant functioned for 1½ days.

rabbit immunized to the donor skin by previous transplantation. He found that lymph node extracts, spleen, or liver from the immunized animal were also ineffective in preventing growth of donor skin. Allgower and co-workers confirmed these findings and further demonstrated that the addition of graft bed tissue from an immunized animal was ineffective in preventing growth of donor skin in tissue culture. Dempster (9) removed blood from kidney transplant recipients when the transplant ceased to function in 3 dogs and injected 150 cubic centimeters of serum obtained from this blood into the donor. Examination of the donor's remaining kidney 1 week later revealed no abnormality. Billingham, Brent, and Medawar (3) found that killed lymph nodes, whole blood, white blood cells, or serum from an immunized animal were ineffective in transferring immunity to a nonimmunized animal. Inasmuch as only viable re-

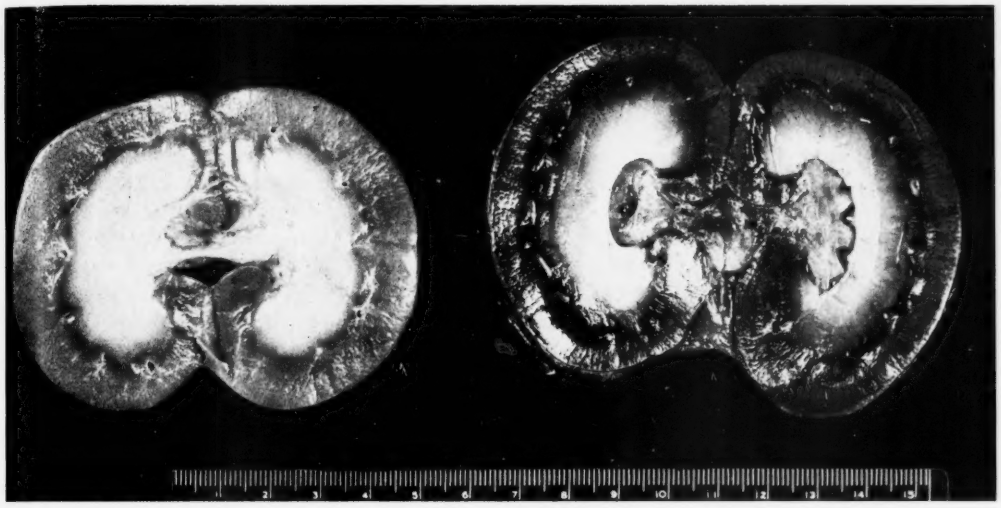

FIG. 6. Precross-circulated primary kidney homotransplant. Note cortex darkness in transplant compared to normal, at left. Microscopically, this darkness is hemorrhage.

gional lymph nodes from an immune animal were found to transfer immunity to a normal animal, it was thought that the transplanted lymphoid tissue produced antibodies and that the effect was not due to antibody content in the node at time of transplantation.

Our results with plasma and spleen extract injections from an immunized animal into the renal artery of the remaining donor kidney also failed to produce changes in that kidney. By injecting directly into the renal artery, antibody filtering by other organs which might share antigens with the kidney was avoided. Therefore, it appears that the total antibody content circulating in the blood stream of an immunized animal at any one moment is probably not sufficient to produce a transplant reaction. The ineffectuality of spleen extracts in producing transplantation reactions of the remaining donor kidney may also be explained on a relative dosage basis.

It is perhaps more difficult to explain the findings of experiments in which cross circulation was performed after the resection of the transplant. The cross circulation technique used resulted in the movement of several hundred cubic centimeters of blood between the dogs each minute, and studies with radioactive chromium tagged red blood cells (11) have demonstrated that equilibration between the two blood streams occurs between 5 and 15 minutes after cross circulation is started. There seems to be little question of the admixing of the blood stream of the 2 animals. The absence of changes in the remaining donor kidney following these cross circulation procedures has three possible explanations. It is possible, as in the case of the plasma injections, that the kidney was not exposed to enough antibody. However, Dempster (9) has shown that a secondary kidney transplant may show changes in a few hours or even less, and 1 cross circulation in this study was carried out for as long as 24 hours in a previously immunized pair. Perhaps the most likely explanation is that arterial blood from the immunized animal passes through the lungs of the donor before reaching the remaining kidney. Simonsen (29) has demonstrated that previous transplantation with either skin or spleen will result in immunization to a future kidney transplant in dogs showing that similar antigens are present in

these tissues. In the cross circulating experiments, therefore, the antibody-containing recipient blood is exposed to a whole series of organs and tissues with shared antigens, this diluting the effect of the antibody. The lungs in particular might be expected to be potent filters of antibody, although no gross or microscopic changes were observed. By the time antibody-containing blood reaches the remaining donor kidney, sufficient antibody has been removed to abort its damaging effect. A third possible explanation for this finding is that there is a protective substance circulating in the blood stream of the donor animal, stabilizing his tissues against antibody formed against his tissue. It is interesting that cross circulation alone did not result in changes in the kidneys of dogs.

In the experiments of Part III, previous blood or plasma transfusions did not give immunity, and kidney transplantations following these transfusions behaved like primary homotransplants. Medawar (25) found that massive intravenous infusions of blood did not immunize the recipient against future skin grafts from the donor in rabbits. Intravenous injection of white blood cells were also relatively ineffective in producing immunity, although intradermal injections were very effective.

Cross circulating 2 animals prior to transplantation, however, resulted in a very effective immunization. Secondary transplant changes—very short functional periods, with massive interstitial hemorrhage and tubular necrosis—were more marked in these series of precross-circulated animals than in a previous set of secondary kidney homotransplantations performed in this laboratory (13). As short a period of cross circulation as 5 minutes was sufficient to immunize, and second-set phenomena following cross circulation were observed when transplantation was performed as late as 28 days after cross circulation. It is evident that some antigenic substance or substances passed from one animal to another and resulted in antibody production to them.

In attempting to delineate the portion of the blood responsible for immunization, red blood cells appear most unlikely. Kozelka, studying skin homografts in the domestic fowl, concluded that homograft survival has nothing to do with blood groups. Haddow found that red blood cell groups had no relationship to transplantation survival of fowl sarcoma. Medawar (24) concluded that previous blood transfusions do not result in immunity to future skin grafts, and Woodruff and Allan stated that blood groups have little to do with skin homograft survival in humans.

Much more likely as immunizing substances in the blood stream are the white blood cells. Medawar (24) found that just 3 intradermal injections of white blood cells from 4 cubic centimeters of blood result in complete immunity to future skin grafts in rabbits. It seems quite likely, therefore, that white blood cells and skin have antigens in common. However, immunizing possibilities are not limited to the cellular elements of the blood stream.

Cumley and Irwin demonstrated by absorption experiments that human serum from each individual has a specificity of its own. Each serum contains antigenic components that serve to identify it from other serums, although there is no difference by conventional technique in the plasma proteins of the different sera. Host body tissues undergo a constant cycle of cellular breakdown and regeneration, and certainly these breakdown products of tissues find their way into the blood stream. It is possible that such breakdown products, representing a sort of "antigenic mosaic" of the body tissues, act either as antigens or haptenes to immunize a recipient against future graft material. Gell and co-workers demonstrated that extremely simple chemical compounds injected in guinea pigs can result in skin sensitization. It is suggested that these simple compounds combined with body protein in vivo to form a complete antigen. It is impossible, from the material of this study to conclude whether the white cells or serum

protein constituents have greater significance in the immunizing process.

Preliminary experiments with transplantation and cross circulation at the same time indicate that there may be some protection of the transplant by the addition of the cross circulation. In the pair of animals cross circulated for 68 hours, 10 days prior to transplantation plus cross circulation, a very violent second-set transplant reaction could have been expected (13). However, the transplant secreted urine for 3 days, and at the end of that time was virtually normal on histologic examination. After separation from cross circulation the transplant went on to rapid necrosis. Either antibodies produced by the recipient animal are diluted in the body of the donor, or some "protective substance" circulating in the blood stream of the donor must be hypothecated to explain these findings. It is interesting that Kamrin and Kamrin found survival of kidney homotransplant slices in rats when the rats were placed in parabiosis.

CONCLUSIONS

1. Injection of plasma or spleen extracts from kidney transplant host into the renal artery of the remaining kidney of the donor at the time of transplant destruction does not result in changes in the remaining donor kidney.

2. Cross circulation of kidney transplant donor with recipient for one long period or several short ones during function of the transplant or after its destruction and removal does not result in changes in the remaining donor kidney.

3. Cross circulating 2 animals prior to kidney transplantation for as short an interval as 5 minutes results in an immune state in the animals so that future kidney transplantation behave as secondary transplants.

4. There is some evidence that cross circulating 2 animals continuously after transplantation stabilizes the transplant in some manner so that the homotransplant reaction is either delayed or inhibited.

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POSTOPERATIVE THROMBIN PRODUCTION

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THE OBSERVATION that elevated amounts of thrombin may be recovered from the plasma of rabbits with experimental thrombosis and patients with various diseases prompted this investigation of the thrombin values associated with postoperative thrombosis. Embolic complications often occur without preceding clinical evidence of intravascular clotting, although autopsies on bodies of patients who had been previously bedridden reveal high incidence of venous thrombosis.

It was suspected that fibrin formation might be associated with increased thrombin production and that the level of circulating thrombin might then rise because thrombin acting enzymatically is not consumed appreciably during clotting. Free thrombin, however, does not persist in the circulation, but is apparently inactivated forming inert complexes. In vitro, these complexes have been dissociated and active thrombin recovered (9).

MATERIALS AND METHODS

Patients from the Third Surgical (New York University) Division at Bellevue Hospital were divided into two groups. Group I included patients with uneventful recovery. They ambulated a few hours after surgery. Their temperatures remained under 100 degrees F. and were normal by the second day. Group II consisted of patients who (a) were restricted in their activity by bed rest, immobilization in casts, or by other means; (b) developed hypotension in the early postoperative period; or, (c) developed fever, infection, or clinical signs of thrombosis during the first 5 postoperative days. In this group complications appeared by the fifth postoperative day. The clinical data are summarized in Tables I and II.

The following determinations were made before and on approximately every other day for 10 to 40 days following operation: plasma thrombin, prothrombin, fibrinogen, platelet count, erythrocyte sedimentation rate, and fibrinogen B. The patients remained under close clinical scrutiny throughout the study period.

The thrombocyte count and erythrocyte sedimentation rate were done on venous blood. For the remaining studies plasma was separated from a mixture of 9 parts of blood drawn into a silicone coated syringe containing 1 part of 3.8 per cent sodium citrate. A No. 19 dodecyl ammonium chloride coated needle was used for venepuncture. Only nonfrothy specimens were examined.

Thrombin recovery was accomplished by the procedure described previously (8) with these modifications: the substrate for testing thrombin activity was bovine fibrinogen (fraction I of Armour) purified by repeated ammonium sulfate precipitation as described by Ferguson, and made up to 0.2 per cent in a 0.2 molar solution of veronal buffer in physiologic saline. Suitable portions of the reagent were quick frozen at −60 degrees C., stored at −20 degrees C., and thawed at 37 degrees C. whenever needed. The unit of recoverable thrombin was defined as the dilution giving rise to granularity of this substrate in 15 seconds at 18 degrees C. When dilution of the recoverable thrombin became necessary to read the end point, the procedure was repeated with saline diluted plasma.

Plasma prothrombin time was determined on plasma diluted 1:5 with saline using simplastin as the source of thromboplastin. The

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TABLE I.—CLINICAL SUMMARY OF GROUP I PATIENTS WITH UNCOMPLICATED POSTOPERATIVE COURSE

Patient No.	*Diagnosis and operative procedure*	*Age, yrs.*	*Preoperative recoverable thrombin, units*
1	Salpingo-oophorectomy for eccyesis	37	29
2	Appendectomy for acute appendicitis	23	8
3	Herniotomy and bottle operation for inguinal hernia and hydrocele	74	9
4	Sclerosis of a 3 inch segment of great saphenous vein with morrhuate	64	13
5	Subtotal gastrectomy for bleeding from telangiectasia of stomach	20	21
6	Subtotal gastrectomy for peptic ulcer	56	7
7	Stripping and multiple ligation of varicosed veins	69	16
8	Cholecystectomy, transduodenal sphincterotomy for chronic cholecystitis and chronic pancreatitis	54	15
9	Excision of keloids	23	13
10	Sclerosis of a segment of great saphenous vein with morrhuate	62	20

clotting time was converted to per cent of normal prothrombin activity from a dilution curve made with mixtures of normal plasma and saline (7).

Plasma fibrinogen concentration was estimated by recalcifying 1 milliliter of plasma, washing the clot three times in a 0.9 per cent sodium chloride solution, dissolving it in 1 milliliter of a 5 per cent solution of sodium sulfite, and precipitating with 0.7 milliliter of 10 per cent trichloracetic acid. The turbidity of a mixture of 0.2 milliliter of dissolved clot, 0.7 milliliter of 10 per cent trichloracetic acid, and 2.7 milliliters of 0.5 per cent methocel added in this order at 37 degrees C. was linearly proportional to the concentration of protein between 2 and 20 milligrams per milliliter. A Klett Summerson photoelectric colorimeter with a blue filter was used to determine the turbidity of the solutions. A mixture of 0.2 milliliter of sodium sulfite, 0.7 milliliter of trichloracetic acid, and 2.7 milliliters of methocel was used as the blank. The procedure was standardized by comparison with Kjeldahl nitrogen determinations.

The thrombocytes were counted in venous blood by the Reese-Ecker method (12). No dye was added to the diluting fluid, and the formaldehyde concentration was increased to 0.5 per cent. Counts were made within one-half hour of venepuncture.

The blood sedimentation rate was determined by Wintrobe's method using as anticoagulant 6 milligrams of ammonium oxalate and 4 milligrams of potassium oxalate for 5 milliliters blood. The packed cell volume was determined after centrifugation of the blood sedimentation tubes at 3,000 revolutions per minute for 45 minutes. The results were used in calculating the plasma dilution when liquid anticoagulants were employed.

Fibrinogen B was determined by the method of Voorhees and Pulaski. Results were graded 1+ for light precipitates, 2+ for moderate precipitates, and 3+ for heavy precipitates. The test was carried out at 18 degrees C.

RESULTS

The results are shown in Figures 1 to 5 and in Tables I and II. Differences were considered significant when they exceeded 2½ times the standard error.

Recoverable thrombin. The recoverable thrombin rose after surgery in group I (uncomplicated) patients to a maximum on the third postoperative day. It was significantly elevated above the normal as well as the preoperative level from the first to the seventh postoperative day and returned to normal on the tenth postoperative day.

In group II, the recoverable thrombin was significantly elevated above normal before operation. A slight rise occurred postoperatively but it was less than 2½ times the standard deviation. Abnormally high recoverable thrombin titers persisted as much as 40 days after surgery in patients who were still sick or in casts.

The highest postoperative values of recoverable thrombin (up to 69 units) were noted in patients with either clinical thrombotic disease or with chronic infectious disease. The magnitude of the surgical procedure was not reflected in a postoperative increase in recoverable thrombin.

TABLE II.—CLINICAL SUMMARY OF GROUP II PATIENTS WITH COMPLICATED POSTOPERATIVE COURSE

Patient No.	*Diagnosis and operative procedure*	*Preoperative therapy and associated diagnoses*	*Age, yrs.*	*Preoperative recoverable thrombin, units*	*Postoperative complications and degree of activity*
1	Smith-Petersen nailing for fractured hip	Russel traction 2 days; parkinsonism	62	25	Bed rest; venous thrombosis 6th day; heel, hip, back decubiti 15th day
2	Smith-Petersen nailing for fractured hip	Russel traction 3 days	65	27	Bed rest; pneumonia 1st to 9th day. Venous thrombosis 14th day aseptic necrosis of femoral head
3	Smith-Petersen nailing for fractured hip	Russel traction 2 days; auricular fibrillation	83	47	Auricular fibrillation; hypotension during surgery; venous thrombosis and pulmonary embolism 3rd day
4	Smith-Petersen nailing for fractured hip	Russel traction 2 days	47	30	Bed rest; pneumonia 3rd day; wound infection 5th day; refracture 14th day
5	Smith-Petersen nailing for fractured hip	Russel traction 9 days; delirium tremens	50	20	Fever unknown etiology for 6 days postoperatively; bed rest 1st to 9th day
6	Midthigh amputation for arteriosclerotic gangrene	Penicillin, priscoline for 9 days	82	59	Bed rest; sacral decubitus 15th day; infection of stump on 15th day; bed rest 1st to 10th day
7	Below knee amputation for arteriosclerotic gangrene	Terramycin, sympathetic blocks	64	69	Bed rest for 10 days, gangrene of flaps on 6th day
8	Open reduction of fractured tibia	None	54	19	Immobilized in full leg cast
9	Laminectomy to decompress cord from metastatic sarcoma	Reticulum cell sarcoma; paraplegia	28	18	Paraplegia (lower extremities)
10	Former graft for skin avulsion; open and closed reduction of multiple fractures; casts	None	41	15	Immobilized in casts; infection of graft detected on fifteenth day
11	Transplantation of hepatic ducts into stomach for carcinoma of common bile duct	Terramycin, vitamin K; icteric index 136	58	23	Bed rest and limited ambulation for 7 days

TABLE III.—PATIENTS WITH CLINICALLY EVIDENT THROMBOSIS POSTOPERATIVELY

	Days after surgery									
	Preop.	*1*	*2*	*3*	*5*	*6*	*9*	*12*	*14*	*15*
Patient 1:										
Recoverable thrombin (unit/ml. plasma)	47	40	thr.*	47						
Fibrinogen B	+	++		++						
ESR (mm./hr.)	38	46		33						
Plasma fibrinogen (mgm./ml. plasma)	6.8	9.6		11.0						
Plasma prothrombin activity (per cent normal)	110	163		163						
Thrombocyte count, per cu. mm. bld.	216,000	170,000		180,000						
Patient 2:										
Recoverable thrombin (unit/ml. plasma)	27	46		44		30	35	47	thr.*	44
Fibrinogen B	++	++		++		++	++	++		++
ESR (mm./hr.)	19	28		35		24	22	21		18
Plasma fibrinogen (mgm./ml. plasma)	4.9	5.2		5.3		6.7	7.6	8.3		7.9
Plasma prothrombin activity (per cent normal)	125	125		135		118	120	125		110
Thrombocyte count, per cu. mm. bld.	190,000	170,000		142,000		180,000	216,000	236,000		232,000
Patient 3:										
Recoverable thrombin (unit/ml. plasma)	25	30		42	38	thr.* 37	38	27		37
Fibrinogen B	+++	+++		+++		++	+++	+++		+++
ESR (mm./hr.)	32	34		33	32	30	30			
Plasma fibrinogen (mgm./ml. plasma)	5	6.8		7.7		7.1	7.1			
Plasma prothrombin activity (per cent normal)	130	100		100		128	125			
Thrombocyte count, per cu. mm. bld.	220,000	204,000		180,000	212,000	182,000	182,000			

*Thrombosis—criteria for diagnosis: plantar, ankle, or leg edema, calf tenderness, pain on dorsiflexion, dilated superficial veins, fever, rapid pulse.

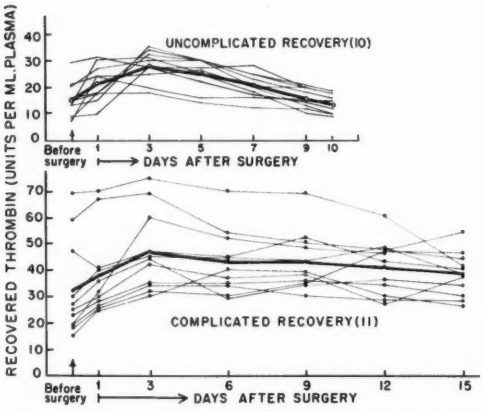

FIG. 1. Plasma recoverable thrombin after surgical operation in 10 patients with uncomplicated recovery and in 11 patients with complicated recovery. The heavy line represents the average for the group.

Plasma prothrombin. Prothrombin activity of diluted plasma did not change significantly in either group.

Plasma fibrinogen. Plasma fibrinogen concentration in group I rose above the preoperative average after surgery. The elevation was significant from the third through the seventh postoperative day.

Group II showed elevated fibrinogen concentration before operation and a slight but significant rise on the sixth through the twelfth day postoperatively.

Neither group exhibited a return to the preoperative average during the observation period.

Thrombocyte count. The thrombocyte count in both groups dropped after surgery to a low on the third postoperative day. It remained significantly depressed below the preoperative mean from the third to the sixth day. Postoperative thrombocytosis as reported by Wright was noted on the ninth and tenth day in group I. It was not seen in group II.

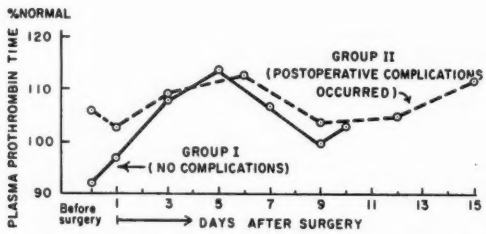

FIG. 2. Average plasma prothrombin time after surgical operation for a group of 10 patients with uncomplicated recovery and a group of 11 patients with postoperative complications.

Sedimentation rate. The postoperative blood sedimentation rate was elevated in both groups. In group I the peak was reached on the fifth postoperative day with a significant elevation above the preoperative average from the third day on. Observations were discontinued on the tenth day. Wright has shown that in a similar group of patients the blood sedimentation rate returned to normal by the twenty-first postoperative day.

In group II the blood sedimentation rate was high throughout the observation period. A significant elevation above the preoperative average occurred on the third postoperative day and persisted through the fifteenth day.

Fibrinogen B. In group I a trace of fibrinogen B was found in 2 patients on the first postoperative day and none thereafter.

In group II, only the 6 patients with infection had fibrinogen B persistently. Immobilized patients developed positive reactions only several days after surgery. Patients who developed clinical thrombosis during the observation period also suffered from infection and showed fibrinogen B throughout.

Although there was an average elevation of recoverable thrombin, fibrinogen, and sedimentation rate during the postoperative period, the degree of elevation did not correlate in individual patients.

Three patients in group II developed clinically evident thrombosis postoperatively (Table III). One patient developed signs of a pulmonary embolus on the third postoperative day. The alterations in plasma recoverable thrombin, prothrombin, fibrinogen, thrombocyte count, and sedimentation rate that occurred in these 3 patients were not different from the changes that occurred in the other patients of group II. The advent of discernible thrombosis was not ac-

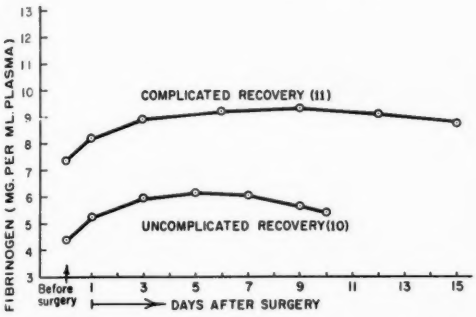

FIG. 3. Average plasma fibrinogen concentration after surgical operation in 10 patients with uncomplicated recovery and in 11 patients with complicated recovery.

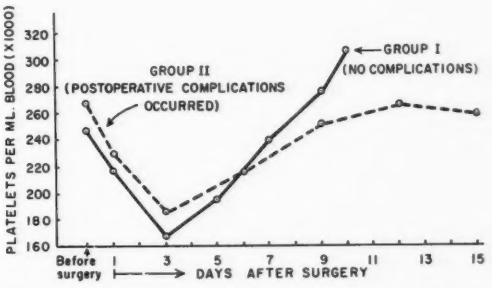

FIG. 4. Average thrombocyte counts after surgical operation for 10 patients with uncomplicated recovery and 11 patients with postoperative complications.

companied by any alteration in the pattern of the determinations.

DISCUSSION

The postoperative rise in recoverable thrombin offers direct evidence of accelerated thrombin formation. The elevation in thrombin production did not correlate with the magnitude of the surgical operation or the prothrombin concentration. The mean prothrombin activity was above normal only once during the follow-up period in each group, yet the recoverable thrombin was elevated for 5 days in group I and throughout the observation period in group II. One patient, after a pulmonary embolus, was given dicumarol until the prothrombin activity fell to 15 per cent of normal. Nevertheless, recoverable thrombin remained high.

Since the postoperative alterations in sedimentation rate, recoverable thrombin, and plasma fibrinogen were not concomitant in individual patients, it is unlikely that these alterations were due to a common factor.

High preoperative mean recoverable thrombin was observed in patients of group II, all but 2 of whom had chronic disease or trauma before surgery. The 3 patients who developed postoperative thrombosis were in this group. Since the majority of patients of group II did not develop clinical thromboembolic complications, recovery of thrombin did not presage that complication. Nevertheless, the candidates for thromboembolism were indicated. Since none of the patients with normal preoperative recoverable thrombin developed postoperative thrombosis, the test may perhaps help in selecting the patients who require special prophylactic care. It may also define more closely the predisposing factors that lead to postoperative thrombosis.

The causes of increased postoperative thrombin formation are unknown. Thrombin produced locally at the site of injury as part of normal hemostasis may account for some. Another source exists, however, because the peak of elevation is not reached until the third day and lasts until the seventh day even in those patients with uneventful

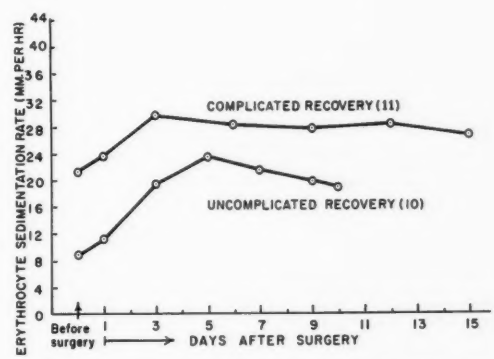

FIG. 5. Average erythrocyte sedimentation rate (corrected) after surgical operation in 10 patients with uncomplicated recovery and in 11 patients with complicated recovery.

recovery from operation. This delayed elevation may be caused by increased prothrombin conversion due to excess thromboplastic substance, accelerator proteins, or the establishment of a foreign surface, e.g., fibrin plugs, damaged endothelium in the vascular system. Such surfaces have been shown to facilitate platelet disintegration and thus promote thrombin formation. Similar procoagulant factors can accelerate thrombin production in the presence of infection and inflammation.

The harmful effect of stasis upon the fluidity of blood was known to Virchow. Less effective dilution of prothrombin converting factors and endothelial injury due to local hypoxia probably account for increased thrombin formation in immobilized patients. The disintegrating effect of anoxia upon venous endothelium was demonstrated by O'Neill, and the clot promoting role of damaged endothelium was shown by Ribbert.

Increased coagulability of the blood was not associated with the onset of clinical thrombosis in our patients. The beginning of thrombosis may depend more upon a balance of local factors, that is, coagulability of the blood (procoagulant and anticoagulant components), rate of blood flow (adequate oxygenation of endothelium and dilution of procoagulant factors), and direct endothelial trauma.

While prophylactic anticoagulant therapy as advocated by Barker and Milch and associates reduces thromboembolic complications, early ambulation, deep breathing, prevention of shock and hypoxia, exercise of the lower extremities, management of cardiac decompensation, as pointed out by Allen, are essential postoperative measures.

SUMMARY

Plasma recoverable thrombin, prothrombin, fibrinogen, erythrocyte sedimentation rate, thrombocyte counts, and fibrinogen B have been measured in surgical patients with and without various complications in an effort to detect and anticipate thromboembolic accidents.

Six of the 11 patients with the postoperative period complicated by infection or recognized thrombosis had elevated recoverable thrombin concentration preoperatively; 1 of the 10 patients with a normal postoperative course had an elevated recoverable thrombin concentration preoperatively.

Six of the 11 patients with the postoperative period complicated by infection or thrombosis exhibited fibrinogen B preoperatively; 2 of the 10 patients with a normal postoperative course exhibited traces of fibrinogen B preoperatively.

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PERONEAL TRANSLOCATION FOR PARALYSIS OF PLANTAR FLEXOR MUSCLES

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IN THE YEARS 1931 AND 1932, von Baeyer (1, 2) discussed the advantages of translocation of the tendon of the peroneus longus as compared with transplantation of that tendon to alleviate disability resulting from weakness or paralysis of the plantar flexors. The advantages claimed are: (1) In translocating the tendon, structures are displaced without disturbing their continuity. (2) Suture of a tendon is avoided. (3) The period of immobilization after translocation is shorter than it is after transplantation. (4) The muscle is immediately placed under tension, which prevents loss of strength. Von Baeyer reported animal experimentation in which increased tension on the tendon produced hypertrophy of the muscles, rather than the atrophy which was claimed by some workers.

In 1944, Bickel and Moe reported a study of 13 cases in which procedures similar to those advocated by von Baeyer were done. The results were as follows: 1 excellent, 3 very good, 4 good, 2 fair, and 3 poor.

The indication for the operation is paralysis, or such weakness of the plantar flexors that the results are as follows: (1) The patient limps because of inability, in walking, to "toe-off"; that is, in walking he cannot exert the customary upward and forward thrust from the anterior part of the foot. (2) The patient cannot climb stairs or walk rapidly. (3) Severe talipes cavus and calcaneal deformities tend to develop.

In order to stop a patient's limping due to weakness of the plantar flexor muscles, he must regain sufficient power to enable him to stand on the affected foot, with the heel raised from the floor. Because the leverage available is not great and the weight of the entire body is to be lifted, much muscular power is required. Therefore, if the tendon of the peroneus longus is to be translocated, the muscle must be normal or nearly so in order to possess the required power in its new position. Any power which the gastrocnemius muscle can exert enhances the likelihood of success of the procedure.

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EXPERIENCE IN 30 CASES

In the work here reported, 34 operations were performed on 30 patients, 17 of whom were females and 13, males. Their average age was 8½ years; the oldest was 28 years of age and the youngest, 6 months. All but 2 of the patients had had poliomyelitis. One of these 2 patients had sustained a nerve injury, and the feet of the other, the youngest of the group, were severely and congenitally deformed. The patients who had had poliomyelitis underwent surgical operation an average of 27 months after the end of the acute stage of the disease. Patients were followed for an average of 26 months after operation. The shortest time any patient was followed was 7 months and the longest, 72 months. Nine of the translocation operations were performed for the typical limp due to weakness of the gastrocnemius-soleus muscles without deformity. Deformities in addition to the limp were the reasons for the other 25 operations, as follows: calcaneal deformities, 6 operations; talipes valgus, 4; talipes cavus, 3; and combinations of the three types of deformities just mentioned, 12 operations.

TABLE I.—RESULTS IN 34 TRANSLOCATIONS OF THE PERONEUS LONGUS TENDON IN 30 PATIENTS

Result	*Operations*	*Per cent*
Excellent	12	35.3
Good	13	38.2
Poor	7	20.7
Failure	2	5.8

Evaluation of the results of the procedure was based on the following criteria: (1) If the patient was able to stand on the affected foot with heel elevated from the floor, and if deformity was reduced or absent, the result was considered excellent. (2) If there was considerable increase in power with lessening of calcaneal deformity, or no change, the result was considered good. (3) If there was little change in power and the deformity was unchanged the result was considered poor. (4) If there was little or no change in power and the deformity was worse than before operation, the treatment was considered to have failed. The results of the operations, graded as described, are shown in Table I.

Postoperative complications were as follows: In 6 cases some varus deformity resulted from removal of the strong everting component in the peroneus longus muscle; thereby imbalance was established between the invertors and evertors of the foot. In 3 cases the incisions did not heal primarily. In 1 case an equinus deformity developed and, in 1, cellulitis prolonged convalescence.

Surgical procedure. From the toes to the groin, the extremity was prepared with an antibacterial sudsing preparation of which the registered name is *p*HISOHEX; it contains sodium octylphenoxyethoxyethyl ether sulfonate, lanolin cholesterols, petrolatum, and hexachlorophene. Sterile stockinet then was rolled the length of the limb. The extremity was exsanguinated with an Esmarch bandage, and another Esmarch bandage was used as a tourniquet around the thigh. An incision was made along the line of the tendon of the peroneus longus, in the skin of the lower lateral aspect of the leg, and was carried down almost to the point where the tendon disappeared into the sole of the foot. A second incision, made over the lower portion of the Achilles tendon, extended downward over the heel. The tendon of the peroneus longus was freed from its sheath. On the posterior aspect of the lateral malleolus, this tendon lies behind that of the peroneus brevis and, on the lateral aspect of the calcaneus, the tendon of the peroneus longus lies below that of the peroneus brevis.

Through the second incision, a groove was made on the posterior and plantar surfaces of the calcaneus. For this procedure, a narrow osteotome and small gouge were used. It was necessary to sacrifice some of the central fibers of the Achilles tendon.

The two incisions were connected subcutaneously by means of a sharp periosteal elevator which is held as close to bone as possible. By use of 2 buttonhooks the position of the tendon of the peroneus longus was changed so that it lay in the groove prepared for it in the calcaneus. In order to accomplish this, the foot had to be sharply plantar-flexed. The tendon compartment beneath the lateral malleolus was repaired to prevent the tendon of the peroneus brevis from riding up over the malleolus. The subcutaneous tissues were approximated with interrupted sutures of fine, plain catgut and the skin edges with interrupted fine sutures of a plastic material for which the trade name is zytor.

The dry dressings which were used were kept in place with sterile sheet wadding. A cast was applied from the tibial tubercle to the base of the toes, with the foot in plantar flexion. To allow for postoperative swelling, a strip of plaster 1 inch wide was removed from the anterior aspect of the cast. The strip started 2 inches from the upper end of the cast and extended to within 2 inches of its lower end. The tourniquet was removed.

Postoperative treatment. At the end of 3 weeks the cast and sutures were removed and physical treatment was started. This treatment consisted of use of whirlpool baths followed by deep sedative massage, stretching of the translocated tendon, re-education exercise of the muscle in its new function of

pure plantar flexion, and progressive resistive exercises to increase power. Usually about 4 to 6 weeks of treatment were required to stretch the tendon out to the point where the foot could be brought to a right angle with the leg. Walking tended to stretch the muscle to the appropriate length. The average duration of treatment in the cases on which this report is based was 4½ weeks. Most patients were treated daily; some received 2 treatments daily.

COMMENT

We believe that this procedure is a good one for treatment of weakness of the gastrocnemius and soleus muscles and that the reasons for its effectiveness are essentially the same as those given by von Baeyer. The surgical operation can be done relatively early in the chronic stage of poliomyelitis and a long period of immobilization is not required. The translocated tendon requires little re-education in its new position because the peroneus longus normally has a strong component of plantar flexion. The question of proper tension on the tendon is not a problem in translocation as it can be in transplantation. We believe the procedure is satisfactory so far as preventing a deformity is concerned and that it will decrease the limp in a fair percentage of cases.

The failures we met with usually were due to complete paralysis of the plantar flexors or lack of normal power of the translocated muscle. Sometimes it is difficult to determine the power of the peroneus longus muscle of a young patient. The complications of the procedure apparently are not serious. However, it is important to select the patients carefully. The operation should not be done unless the peroneus longus muscle is normal or nearly so.

SUMMARY

Thirty patients whose plantar flexor muscles were weak or paralyzed were subjected to 34 operations for translocation of the tendon of the peroneus longus muscle. In all but 2 of the cases, the condition followed poliomyelitis. Good or excellent results followed 73.5 per cent of the operations, and poor results or failure followed 26.5 per cent of them. However, the classification of poor results included those in which deformity was arrested; therefore, 94.2 per cent of the operations were followed either by improvement of deformity or by no further progression of it.

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THE RELATIONSHIP BETWEEN PLASMA SODIUM CONCENTRATION AND THE STATE OF HYDRATION OF BURNED PATIENTS

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EXTENSIVELY BURNED PATIENTS frequently have serious fluid and electrolyte abnormalities after the third postburn day. The use of currently accepted regimens of therapy is associated with a lower than normal plasma sodium concentration[1] at the end of the first or second postburn day.[2] The significance and causes of this hyponatremia are not understood, and attempts at increasing the plasma sodium with isotonic or hypertonic sodium solutions have been made.

Cope has observed that the mild hyponatremia following burns is largely asymptomatic and usually is associated with a good clinical response. It has also been the experience of our group that a plasma sodium in the range of 130 to 135 milliequivalents during the early postburn period is associated with a good physiologic adjustment to the burn injury. On the other hand, a plasma sodium of 145 to 155 milliequivalents is often associated with symptoms of fluid deficits.

In an attempt to delineate the relationship between plasma sodium and the state of hydration of the burned patient, the records of 24 severely burned patients who had metabolic studies were reviewed and analyzed.

CLINICAL MATERIAL AND PROCEDURES

There were 8 survivors and 16 fatalities. The mean total extent of burn was 50 per cent, and the mean extent of third degree burn was 32 per cent. All were healthy and well nourished individuals before burning. They were admitted to the Metabolic Division within 20 minutes to 96 hours after burning. The ages of the patients ranged from 17 to 42 years, with the exception of 3 whose ages were 8, 14, and 65 years. The mean survival time of the fatalities was 22 days. Observations were made for as long a period as 35 days postburn in some of these patients.

Fluid therapy was guided by the Brooke Army Hospital formula (3), which provides for 0.5 cubic centimeter of colloid per kilogram per percentage of burn and 1.5 cubic centimeters of electrolyte solution per kilogram per per cent of burn during the first 24 hours. The therapy actually given to the 24 patients is shown in Table I. On the average, 1,200 cubic centimeters of intravenous dextrose in water or oral water were administered during the first 24 hours. The average sodium concentration of fluids administered during the first 48 hours was approximately 100 milliequivalents per liter. Thus, the initial fluid therapy was accomplished with hypotonic fluids.

The fluid balance was calculated from the following sources: All of the fluid intake was measured. The total volume of transfusions was included in the fluid intake. The fluid output was calculated from the urine and emesis. The urinary output was pooled in 24 hour specimens. The sodium balance was calculated from all sources of sodium intake. Manufacturers' specifications were

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[1]The plasma sodium concentration will be referred to simply as plasma sodium and will be expressed in mEq. rather than mEq. per liter.

[2]The normal mean plasma sodium ± 1 S.E. in this laboratory is 146 ± 0.4 mEq. per liter.

used for computing the sodium intake from the intravenous fluids. The sodium value used for whole blood was 90 milliequivalents per liter. The contribution of food and formula to the sodium intake was determined by chemical analyses as described previously by Pearson and associates. Only the sodium in the urine and emesis was used to calculate the sodium losses because the sodium content of exudate was not determined in all patients.

Dressings of some of the patients were pooled in convenient periods and washed. Aliquots of the wash water were analyzed for sodium. These data were used in a separate analysis for the estimation of insensible water losses.

The plasma sodium was measured in many blood samples. These were always drawn at the same time in the morning with the patients in the fasting state. All sodium determinations were performed with a Perkin-Elmer flame photometer. In the clinical illustrations, total body water was measured by the deuterium oxide space, and the extracellular fluid volume was estimated by the sucrose space and the thiosulfate space.

OVERALL ANALYSIS OF FLUID BALANCE, SODIUM BALANCE, AND ALTERATIONS IN PLASMA SODIUM

Method of analysis. The relationship between the sodium and fluid balances and the changes in plasma sodium observed in any two consecutive daily analyses was examined. All consecutive daily plasma sodium values were considered in pairs and assigned to one of three groups: group A, the group in which there was no change in the plasma sodium from the first to the second observation; group B, the group in which the plasma sodium increased; and group C, the group in which the plasma sodium decreased (Table II). The assignment to each of the three groups was made according to the direction of the change of the plasma sodium and was made irrespective of the absolute concentration of either the first or second plasma sodium in the pair. On the basis of the precision of the chemical analysis, a change of 4 milliequivalents or more of plasma sodium was considered significant. The total fluid balance, the sodium balance, and the resultant "available nonelectrolyte water" for each 24 hour period were correlated with the alterations in the plasma sodium for that 24 hour period. There were 90 pairs of observations in group A, 31 pairs in group B, and 33 in group C.

The method of calculating the "available nonelectrolyte water" is shown in Table III. For each pair of plasma sodium observations, the mean was calculated, and this was considered representative of the plasma sodium for that 24 hour period. The sodium balance for the day was then divided by the mean plasma sodium for the day in order to

TABLE I.—INITIAL POSTBURN FLUID AND ELECTROLYTE THERAPY

	Time postburn	
Therapy	*Burn to 8 a.m. on the following morning*	*1st postburn day*
Fluid intake, c.c.	6900	6200
Electrolyte solutions, c.c.	3800	3800
Colloid solutions, c.c.	1900	700
Sodium intake, mEq.	700	600
Sodium concentration of administered fluids, mEq./L.	109	99

Mean of 24 patients.

TABLE II.—SUMMARY OF ANALYSIS OF VARIANCE OF FLUID BALANCE AND ALTERATIONS IN PLASMA SODIUM

Group	*A No change*	*B Incr. conc.*	*C Decr. conc.*
No. of paired observations	90	31	33
1st plasma sodium conc.	135	132	140*
2nd plasma sodium conc.	135	139†	133
Mean of 1st and 2nd plasma sodium conc.	135	136	136
Sodium intake	220	295	210
Urinary sodium, mEq./24 hrs.	150	155	145
Sodium balance‡	+50	+120	+60
Fluid intake	5,290	5,010	5,330
Urinary volume	2,670	2,670	2,180
Fluid balance	+2,410	+2,120	+2,920
"Available nonelectrolyte water"	+2,032	+1,318†	+2,494

All data expressed as means
Subgroup analysis of variance was always group A vs. group B or group C.
*Significant at 0.1 per cent level.
†Significant at 1.0 per cent level.
‡Sodium intake minus urinary and emesis sodium.

TABLE III.—METHOD OF CALCULATING "AVAILABLE NONELECTROLYTE WATER"

Samples	*Plasma Na_1 mEq./L.*	*Plasma Na_2 m.Eq./L.*	*Mean plasma $Na_1 + Na_2$ mEq./L.*	*Na balance mEq.*	*Fluid balance c.c.*	*Isotonic fl. bal.* c.c.*	*"Available nonelectrolyte water" c.c.*
1, positive Na balance	138	142	140	+70	+3,000	+500	+2,500
2, negative Na balance	143	137	140	−210	+3,000	−1,500	+4,500

*Isotonic fluid balance $= \frac{\text{Na balance}}{\text{Mean plasma } Na_1 + Na_2} \times 1000$ or as in sample 1: $\frac{+70}{140} \times 1000 = +500$ c.c.

determine the balance of isotonic fluid available to the patient for that 24 hour period. This quantity of isotonic fluid was then subtracted algebraically from the fluid balance. The resultant figure gave the volume of "available nonelectrolyte water."

Results of analysis (Table II). The data from all 24 patients were analyzed by analysis of variance. The "available nonelectrolyte water" in group A (+2032 c.c.) was significantly greater than in group B (+1318 c.c.) but not significantly different from group C (+2494 c.c.). In Figure 1, the correlation between "available nonelectrolyte water" and change in plasma sodium is shown ($r = -0.49$, $P < 0.001$). This relationship suggests that the greater the quantity of "available nonelectrolyte water," the greater the fall in plasma sodium and, conversely, the less the quantity of available water, the greater the rise in plasma sodium.

The means of the first plasma sodium in groups A and B were not significantly different. However, the mean of the first plasma sodium was significantly lower in group A than in group C. At the end of the 24 hour period when the second plasma sodium concentration was measured, the reverse was true: groups A and C did not differ significantly, but the plasma sodium was significantly higher in group B than in group A.

The mean of the first and second plasma sodium of all three groups was 136 milliequivalents. This suggests that under the conditions of therapy in this group of patients the trend was for the changes in plasma sodium to converge at about the 136 milliequivalent level.

The sodium balance, fluid intake, urine volume, and fluid balance did not differ significantly in the three groups. The expected trends, however, were apparent: The fluid intake and fluid balances were, on the average, larger in group C, and the sodium intake and balance were larger in group B than in the other groups. All of these parameters affect the "available nonelectrolyte water" calculation where significant differences can be seen.

ANALYSIS BY TIME PERIODS

Plasma sodium changes were analyzed again by dividing the data into three time periods: days 1 and 2—the acute postburn phase; days 3 to 12—the phase of fluid redistribution; and days 13 to 35—the phase of completion of healing of second degree burns and separation of the third degree eschars (Table IV). In days 1 and 2, the "available nonelectrolyte water" in group C (decreasing concentration) was actually less than in group A (no change).[3] During the other phases, the quantity of "available nonelectrolyte water" in group C was greater than in group A, and in the 3 to 12 day interval this difference was significant. The mean of the first and second plasma sodium gradually decreased in all three groups from 139 milliequivalents at day 1 to 2 to 132 milliequivalents in the period extending from day 13 to the end of the study. The means of the other observations follow essentially the same pattern as in the overall analysis shown in Table II.

COMPARISON BETWEEN SURVIVORS AND FATALITIES

The available data of the 5 patients who died with signs, symptoms, and laboratory

[3]See Discussion.

TABLE IV.—RESULTS OF ANALYSIS OF VARIANCE OF FLUID BALANCE AND ALTERATIONS OF PLASMA SODIUM ACCORDING TO PERIODS OF POSTBURN DAYS

	1 and 2 postburn days			*3–12 postburn days*			*13–35 postburn days*		
	Group A	*Group B*	*Group C*	*Group A*	*Group B*	*Group C*	*Group A*	*Group B*	*Group C*
Days observed	*10*	*3*	*5*	*49*	*19*	*20*	*31*	*9*	*8*
1st plasma Na conc.	140	139	140	135	133	143 ‡	132	130	132
2nd plasma Na conc.	140	144	134 *	135	140*	135	134	137*	127 †
Mean plasma Na conc.	140	141	137	135	137	139	132	132	129
Sodium intake	515	795	450	145	210	165	240	320	180
Urinary sodium	135	135	155	130	135	145	190	255	140
Sodium balance§	+ 345	+ 660	+ 290	+1	+15	+45	+40	+95	+20
Fluid intake	6450	5830	4870	4840	4620	5480	5650	5550	5240
Urinary volume	1230	1060	1120	2300	2550	2260	3700	3730	2660
Fluid balance	+5220	+4780	+3750	+2330	1990	+2660	+1790	+1510	+2210
"Available water"	2812	513‡	1646	2215	1688	2878*	1486	807	2063

Subgroup analysis of variance was always group A vs. group B or group C.
*Significant at 5.0 per cent level.
†Significant at 1.0 per cent level.
‡Significant at 0.1 per cent level.
§Sodium intake minus urinary and emesis sodium.

Group A—no change.
Group B—increasing conc.
Group C—decreasing conc.

evidence of water deficits were reviewed (mean total extent of burn 75 per cent and mean extent of third degree 66 per cent). The average survival time of the fatalities was 6 days. The observations used extended over the first 10 days postburn, except for 1 patient whose observations extended to postburn day 12. The only available data on 3 survivors with a comparable *total extent* of burn were used for purpose of comparison with the data on the patients who did not survive (mean total extent of burn of 68 per cent and mean extent of third degree burn of 30 per cent).

The data are shown in Table V for these 8 patients. The mean plasma sodium in the fatalities was significantly higher than in the survivors. This higher plasma sodium was associated with a much greater sodium intake, a significantly greater urinary sodium concentration, and, surprisingly, an equal volume of "available nonelectrolyte water." Thus, there was no evidence that the higher plasma sodium in the group of deaths was associated with the patients' inability to excrete sodium nor with a decreased amount of "available nonelectrolyte water." Unfortunately, sufficient data are not available for a comparison of the insensible water losses in the deaths and survivors, for it is likely that the greater extent of third degree burn in the deaths contributed to a greater insensible water loss, and hence the quantity of "available nonelectrolyte water" was insufficient for the group of fatalities.

The urinary volume was significantly less in the fatalities than in the survivors, although the fluid intake was of the same order of magnitude. This observation points toward an attempt at conservation of water in the presence of relative hypernatremia.

RELATIONSHIP BETWEEN ABSOLUTE PLASMA SODIUM AND URINARY VOLUME

Because of the association of a high plasma sodium and a lower urinary volume in the patients with fluid deficits, the general relationship between the plasma sodium concentration and the urinary volume was further examined. The data were divided into three groups according to the mean

TABLE V.—DAILY PLASMA SODIUM CONCENTRATIONS AND FLUID BALANCES OVER THE FIRST TEN POSTBURN DAYS IN SURVIVORS AND FATALITIES

	Survivors	*Fatalities*
No. patients	3	5
Mean plasma Na	137§	148
Na intake	295	510
Urinary Na concentration	65†	127
Total urinary Na	160	150
Na balance*	+110	+320
Fluid intake	5520	5771
Urinary volume	2710§	1170
Fluid balance	+2670	+4054
Available nonelectrolyte water	+1849	+1880

All data are expressed as means per day.
*Sodium intake minus urinary and emesis sodium.
†Significant at 5.0 per cent level.
‡Significant at 1.0 per cent level.
§Significant at 0.1 per cent level.

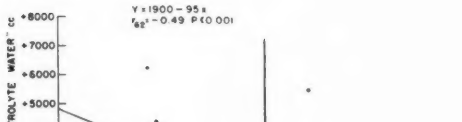


FIG. 1.

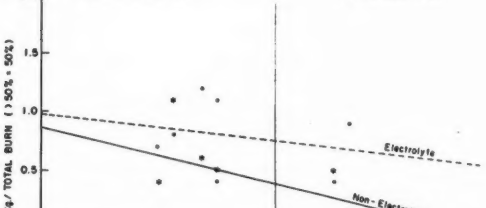

POSTBURN DAYS 1-2
• Electrolyte Fluid
* Non-electrolyte Fluid
r_{62} = −0.2271 P > 0.1
r_{62} = −0.4220 P > 0.1
cc / Kg / TOTAL BURN (>50% + 50%)
Electrolyte
Non-Electrolyte
Δ PLASMA No⁺ (mEq/L)

FIG. 2.

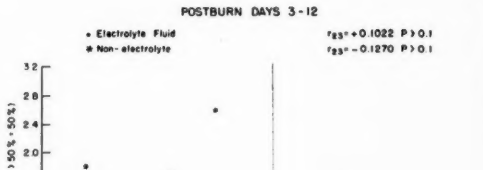


FIG. 3.

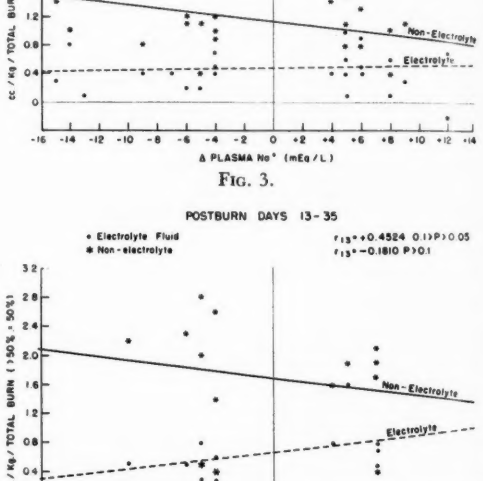

POSTBURN DAYS 13-35
• Electrolyte Fluid
* Non-electrolyte
r_{13} = +0.4524 0.1 > P > 0.05
r_{13} = −0.1810 P > 0.1
cc / Kg / TOTAL BURN (>50% + 50%)
Non-Electrolyte
Electrolyte
Δ PLASMA No⁺ (mEq/L)

FIG. 4.

FIGS. 1, 2, 3, and 4. The lines were fitted by the method of least squares. These correlations are nonsignificant, and an exact functional relationship is not implied.

plasma sodium for any 24 hour period (Table VI). The absolute values chosen were 135 milliequivalents and below, 136 to 145 milliequivalents, and 146 milliequivalents and above. Considering all three groups, the mean fluid intakes did not differ significantly. The mean urine volumes, however, were significantly different; the 146 milliequivalents and above group was associated with a lower urine volume.

ESTIMATION OF INSENSIBLE WATER LOSS

The insensible water loss was calculated from the following equation: Insensible water loss = weight of diet + fluid intake − (weight change + urinary volume + weight of stool + estimated exudate volume + emesis). The exudate volume was calculated as exudate sodium × 1,000 ÷ mean plasma sodium, on the assumption that the concentration of sodium in the exudate is equal to that in the plasma.[4] The results were analyzed in the following time periods: days 1 and 2, 3 to 12, and 13 to 19 (Table VII). The insensible losses from days 1 through 19 were quite constant. The mean insensible water loss for the entire group of observations was 2,670 cubic centimeters per day.

RELATIONSHIP BETWEEN FLUID THERAPY AND PLASMA SODIUM CONCENTRATION

In an effort to clarify the effect of sodium and water therapy on the plasma sodium concentration, the fluids administered were

[4]It is recognized that this assumption is probably valid only during the early postburn period.

considered as being either isotonic electrolyte fluid or nonelectrolyte fluid (free water). The isotonic electrolyte fluid volume was calculated as the total milliequivalents of sodium administered to each patient each day divided by 145 milliequivalents and multiplied by 1,000. This amount of electrolyte fluid was then subtracted from the total fluid intake for the day to obtain the volume of nonelectrolyte fluid. The volume of each of these two types of fluids that was administered for any given day was plotted against the changes of plasma sodium for that same day.

Although the correlation in Figures 2, 3, and 4 are not statistically significant, certain interesting trends are apparent. In the immediate postburn period (days 1 to 2), the administration of electrolyte fluid (145 mEq. per liter) appeared to be associated with a decrease in plasma sodium; the administration of nonelectrolyte fluid appeared to be associated with a somewhat sharper decrease (Fig. 2). In the fluid redistribution phase (days 3 to 12), the amount of electrolyte fluid administered over the entire range of changes of plasma sodium varied little, while the amount of nonelectrolyte fluid administered appeared to be associated with a decrease in plasma sodium (Fig. 3). In the third period (days 13 to 35), there seemed to be an association between increasing quantities of electrolyte fluid and an increasing plasma sodium and between increasing quantities of nonelectrolyte fluid and a decreasing plasma sodium. The ratio of nonelectrolyte to electrolyte fluids administered at the point where there was no change in the plasma sodium was 0.5 to 1.0 cubic centimeter in days 1 and 2, and 2.5 to 1.0 cubic centimeter during the subsequent periods.

PATTERN OF URINARY VOLUME

The commonly accepted sequence of events after burns is that resorption of wound edema begins near the end of the second day and that an abrupt diuresis follows. During this resorption phase, it might appear that fluid intake should be somewhat curtailed in order to prevent rapid overexpansion of the intravascular compartment and pulmonary edema. Such a sequence has been observed only rarely in this institution. In the 24 patients reviewed, the daily urinary volume increased gradually and reached a plateau on the twelfth day (Fig. 5). This pattern of urinary volume is probably a reflection of the fluid therapy that was administered. Following the first 48 hours postburn, sizeable quantities of fluid, largely water, were given. Pulmonary edema was not observed.

TABLE VI.—RELATIONSHIP BETWEEN ABSOLUTE PLASMA SODIUM CONCENTRATION FLUID INTAKE AND URINARY VOLUME

Plasma sodium conc., mEq./L..	135 and below	136–145	146 and above
Mean of 1st and 2nd plasma Na conc.....	130–130	139–139	151–152
Mean fluid intake, c.c.....	5,050	5,227	5,533
Mean urinary volume, c.c....	2,786	2,365	1,558*

*Significant at the 1.0 per cent level.

CLINICAL ILLUSTRATIONS

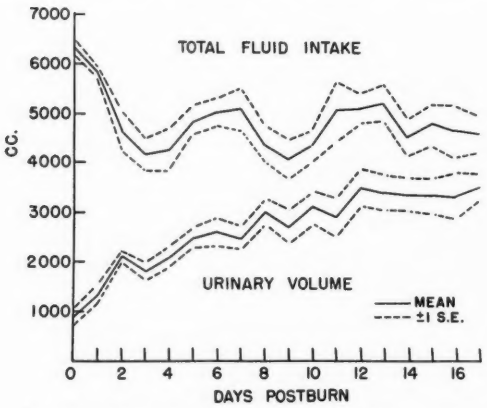
The clinical course, fluid therapy, and laboratory findings are presented in 2 patients in order to illustrate some of these observations.

PATIENT E. B. (Fig. 6). A 24 year old airman sustained a burn of 45 per cent of the body surface, including a third degree burn of 25 per cent of the body surface. Full thickness burns involved the face, the scalp, and both upper extremities; partial thickness burns involved the trunk and the anterior aspect of the thighs. The wounds were cleansed, the face was treated by the exposure method, and the remainder of the burned areas were treated by occlusive dressings. A tracheotomy was performed a few hours after injury.

TABLE VII.—INSENSIBLE WATER LOSS

Postburn days	*Insensible water (mean)*	± *Standard error*
1	2360	±1000
2	2700	± 884
3–12	2800	± 333
13–19	2580	± 341
Mean	2670	± 256

Number of patients—13; mean total extent of burn was 46 per cent; the mean extent of third degree burn was 17 per cent; the total number of patient days analyzed was 198.



FIGS. 5 and 6. Day 0 extended from the time of burning at 2000 hours to 0800 hours the following morning. Total output was used to calculate the balances.

During postburn days 0 and 1, the total fluid intake was 7,750 cubic centimeters and the sodium intake was 770 milliequivalents, a concentration of 99 milliequivalents of sodium per liter. The urinary output was approximately 40 cubic centimeters per hour, and the patient seemed to respond well to treatment.

On postburn day 2, the patient received 1,600 cubic centimeters of fluid, 210 milliequivalents of sodium, a concentration of 131 milliequivalents of sodium per liter.

On the third postburn day, the plasma sodium was 137 milliequivalents per liter, the fluid intake 3,800 cubic centimeters, the sodium intake 326 milliequivalents[5], the total body water (TBW) 46.3 liters (Table VIII), and the extracellular fluid volume (ECF, sucrose space) 20.6 liters.[6] The estimated normal intracellular fluid volume (ICF) for this patient, whose preburn weight was 72 kilograms, was 30.9 liters (43 per cent of body weight). The calculated ICF obtained by subtracting the ECF from the TBW was 25.7 liters, or an estimated deficit of 5.2 liters. During this day, the patient became increasingly restless and violent.

On the morning of the fourth postburn day, the plasma sodium increased to 145 milliequivalents. On this day, the patient was given a large intake of 5 per cent glucose in water, and the plasma sodium on the morning of the following day, the fifth postburn day, decreased to 130 milliequivalents. Thereafter, the administration of ample quantities of electrolyte-free water was continued and the major source of sodium intake was the diet. The plasma sodium remained in the range of 130 to 135 milliequivalents.

The total body water on the seventh postburn day was 56.1 liters with an ECF determination of 21.6 liters; the calculated ICF was 34.5 liters, an increase in ICF of approximately 9 liters over its calculated value on day 3. After day 7, the patient did not present any problem in fluid management, and he recovered.

This case illustrates that after the large sodium and water loads administered in the first 48 hours, the plasma sodium remained within normal limits. During the third postburn day, inadequate amounts of free water were given, a high sodium intake was continued, and the plasma sodium increased. There was laboratory and clinical evidence of an ICF deficit. This was reflected on the fourth postburn day by relative hypernatremia. Continuous therapy with adequate quantities of free water was begun on the fourth postburn day, the plasma sodium decreased to a lower level, and the ICF deficit was corrected.

[5]The high sodium intake resulted chiefly from administration of sodium thiosulfate that was given for the determination of the thiosulfate space.

[6]It is recognized that the sucrose space may not be a valid measure of ECF in burns. In these patients, sucrose and thiosulfate spaces were measured simultaneously, and the values obtained were in very close agreement.

TABLE VIII.—SPACE MEASUREMENTS

	T.B.W. (*L.*)	*E.C.F.* (*L.*)	*I.C.F.** (*L.*)
		PATIENT E.B.	
Estimated normal.....	43.2	12.3	30.9
Postburn day 3.....	46.3	20.6	25.7
Postburn day 7.....	56.1	21.6	34.5
		PATIENT M.F.	
Estimated normal.....	33.3	9.5	23.8
Postburn day 2.....	49.6	20.8	28.3
Postburn day 8.....	33.2	14.0	18.9

*I.C.F.=(T.B.W.—E.C.F.)

PATIENT M. F. (Fig. 7). This 27 year old female sustained a 55 per cent total body surface burn, including 45 per cent full thickness burn and 10 per cent partial thickness burn. Full thickness burns involved the anterior and posterior aspects of the trunk and the thighs; partial thickness loss extended over the hands and face. The wounds were cleansed and débrided, and occlusive dressings were applied to all burned areas except the face.

During the first 48 hours postburn, the patient received 10,240 cubic centimeters of fluid, the sodium intake was 1,344 milliequivalents, and the concentration of sodium in the administered fluid was 131 milliequivalents per liter. The plasma sodium on the morning of postburn day 1 was 135 milliequivalents. The urinary flow was 50 cubic centimeters per hour, and the patient appeared to be making a good response to her injury.

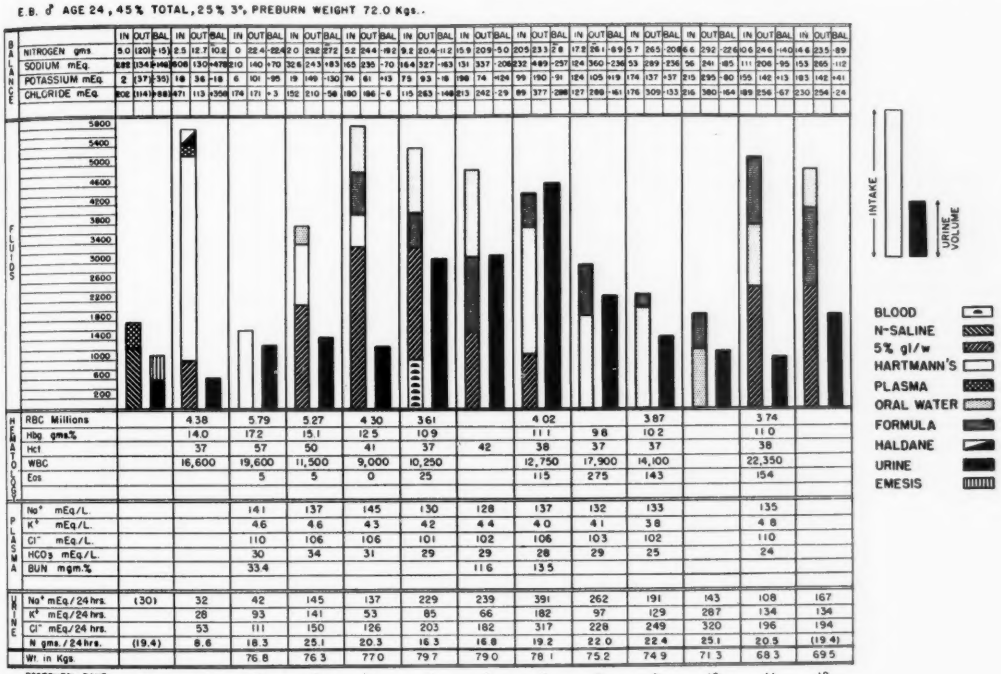


FIG. 6.

On the morning of postburn day 2, the plasma sodium was 140 milliequivalents, the TBW 49.6 liters (Table VIII), and the sucrose space 20.8 liters (thiosulfate space 21.8 liters). The estimated intracellular fluid volume was 28.3 liters. The patient's preburn weight was 72.3 kilograms, and the calculated normal ICF was 23.8 liters (33 per cent of preburn weight). There was, therefore, an estimated expansion of 4.5 liters of intracellular fluid. On this day, the fluid intake was 4,700 cubic centimeters, and the sodium intake was 412 milliequivalents, a concentration of 87 milliequivalents of sodium per liter. The urinary volume was 2.3 liters, and the total urinary sodium output was 456 milliequivalents.

On postburn day 3, the plasma sodium decreased to 132 milliequivalents. The fluid intake was 3,000 cubic centimeters, and the sodium intake was 139 milliequivalents—a concentration of 46 milliequivalents per liter. The urinary volume on this day increased to 2,600 cubic centimeters, and the total urinary sodium excretion on this day was 377 milliequivalents.

From days 4 to 7, her average fluid intake per day was 3,700 cubic centimeters, and the average sodium intake per day was 231 milliequivalents, an average concentration of 62 milliequivalents per liter. The plasma sodium concentration fluctuated between 130 and 138 during this period.

On the morning of postburn day 8, the plasma sodium was 139, the TBW 33.2 liters, and the sucrose space 14.0 liters (thiosulfate space 14.6 liters). The estimated ICF was, therefore, 18.9 liters—a decrease of 9.4 liters from the determination on postburn day 2. The fluid intake on this day was only 1,800 cubic centimeters, and the sodium intake was 368 milliequivalents, a concentration of 204 milliequivalents per liter. The urinary sodium concentration was 151 milliequivalents per liter. The high sodium intake on this day was largely due to the sodium thiosulfate used for the space measurements.

On the morning of postburn day 9, the plasma sodium had risen to 151 milliequivalents, reflecting the high sodium intake and inadequate free water intake of the previous day. The patient was given 6,300 cubic centimeters of intravenous fluids on this day in order to correct her extreme water deficit. The intravenous fluids contained 429 milliequivalents of sodium, a concentration of 68 milliequivalents per liter. The adequate fluid therapy on postburn day 9 resulted in a fall in the concentration of the plasma sodium to 137 milliequivalents. In the ensuing few days, the patient was given adequate amounts of

free water and her state of hydration remained satisfactory.

This case emphasizes that there is a continuing need throughout the postburn period for adequate quantities of free water. Small daily deficits of free water often escape recognition and are not detected until a serious cumulative water deficit has developed.

DISCUSSION

Hyponatremia may be the result of the following causes: (1) excessive sodium loss, i.e., the loss of sodium and water in such a proportion that the concentration of sodium in the losses exceeds the sodium concentration in the extracellular fluid, (2) a shift of sodium from the extracellular fluid to the intracellular fluid without a concomitant shift of water, (3) dilution, i.e., the retention of sodium and water in such a proportion that the concentration of sodium in the retained fluid is less than the extracellular fluid concentration of sodium, or (4) a combination of these factors.

Most of the patients were in positive sodium balance when hyponatremia was observed, and when the sodium balance was negative, the urinary sodium concentration was generally less than the plasma sodium concentration. Thus, a disproportionate sodium loss in relation to water loss was not a factor producing hyponatremia. This was more apparent from examination of the individual records than from the mean data given in the tables.

If a shift of sodium into cells occurred without a concomitant shift of water, this change was largely obscured in the gross clinical correlations of this study. A suggestion of such a shift was obtained in the 1 and 2 day period. This was the only time at which the amount of "available nonelectrolyte water" was actually smaller in the group showing a decrease in the plasma sodium than in the group showing no change (Table IV). In the same interval, a decreasing plasma sodium concentration appeared in the presence of administration of sodium at a concentration of 145 milliequivalents per liter (Fig. 2).

Many of the analyses suggest that dilution may be an important cause of the hyponatremia observed. Except for the 0 to 2 day period, the "available nonelectrolyte water" was always larger in the group showing a decrease in plasma sodium than in the others, and in the 3 to 12 day period, this association was significant. In Table IV, it is also interesting to note that there was a tendency for the mean plasma sodium to decrease with time.

The operation of the normal osmotic regulatory mechanism should prevent hyponatremia. Decreased osmolarity of the extracellular fluid, which is usually associated with hyponatremia, would result in inhibition of antidiuretic hormone secretion, excretion of the excess water, and the return of osmolarity as well as of the plasma sodium concentration to normal levels. That these compensatory mechanisms operated actively when the plasma sodium concentration was high is indicated by the significant reduction in urine volume under this circumstance (Table VI). It was partially effective at low plasma sodium concentrations, since a plasma sodium concentration of less than 130 milliequivalents per liter was observed only rarely. It appears that the osmoregulatory defense mechanisms were set at a lower than normal level.

The significance and causes of hypernatremia are much clearer. Hypernatremia signifies relative water deficit and is caused by insufficient administration of water relative to the water demands. However, since there are some indications that osmoregulation proceeds at lower than normal concentrations of plasma sodium in the burned patient, it is possible that a plasma sodium concentration that is within the range of normal for a normal subject represents "relative hypernatremia" in the burned patient.

Therapeutic implications. The first 48 hours after a burn are characterized by the rapid development of wound edema. The aim of

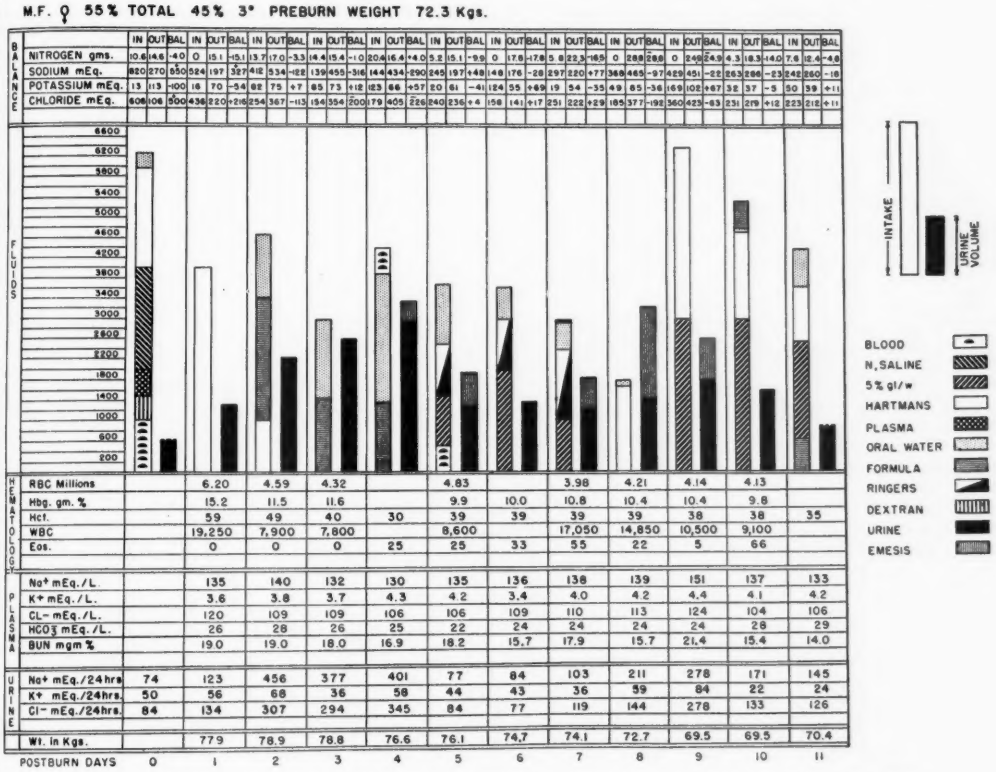


FIG. 7. Day 0 extended from the time of burning at 1000 hours to 0800 hours the following morning. The urine collections of days 0 and 11 are incomplete. Total output was used to calculate the balances.

therapy during this period is to administer colloids and electrolytes at a rate that approximates the obligatory edema formation in the wound and in this way to prevent death due to circulatory collapse. After this time, fluid problems do not cease. On the basis of clinical experience and the data presented in this article, it appears that the administration of adequate quantities of nonelectrolyte water is of cardinal importance. In an individual patient, the water requirements cannot be predicted satisfactorily. It appears, however, that the plasma sodium is a valuable guide to the adequacy of therapy. Slight hyponatremia, with the plasma sodium concentration in the range of 130 to 140 milliequivalents per liter and a mean of approximately 135 milliequivalents per liter, is associated with a good clinical response in nearly all instances. Plasma sodium concentrations of 146 milliequivalents per liter and above are frequently associated with evidence of intracellular water deficit.

CONCLUSIONS

1. Hyponatremia is characteristic of adequately treated burns. It appears to be caused, at least in part, by dilution. It is asymptomatic and can be considered a part of the normal, satisfactory response to a burn.

2. Hypernatremia often occurs in the presence of clinical signs and laboratory evidence of intracellular dehydration. The condition is associated with a lowered urinary volume.

3. After 48 hours, the administration of large quantities of nonelectrolyte water is essential to meet the water requirements of severely burned patients.

4. The plasma sodium concentration is a good index of the adequacy of hydration.

5. The gradual redistribution and excretion of edema fluid in extensively burned patients and the lack of evidence of pulmonary edema in the patients observed emphasize the safety of maintaining an adequate water intake after 48 hours.

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ANTITRYPTIC SUBSTANCES IN EXPERIMENTAL ACUTE PANCREATITIS

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EXPERIMENTALLY acute pancreatic necrosis was first produced in dogs by Claude Bernard in 1856 before the condition was recognized clinically. He injected 15 cubic centimeters of a mixture of sweet oil and bile into the main pancreatic duct, followed by ligature of both ducts. Other workers (quoted by Opie) produced the lesion by injection of zinc chloride, acid gastric juice, cultures of Bacillus coli and other bacteria, diphtheria toxin, papain, sodium hydroxide, and formalin into the pancreatic duct.

The method which has come into common use for the production of acute pancreatitis in dogs was described by Rich and Duff. It consists of the injection of 5 to 10 cubic centimeters of bile aspirated from the gallbladder into the large accessory pancreatic duct. It causes death in a high proportion of animals. Nearly all of the fatalities occur within the first 24 hours, apparently in a condition of shock or toxemia. Of the survivors, some die within a few days of infection in the peritoneal cavity and in and around the pancreas, while others die later with chronic pancreatitis and disorders of intestinal absorption.

The early mortality of acute pancreatitis has been considerably reduced by the use of penicillin and other antibiotics. The present work was undertaken in order to show whether the administration of plasma or whole blood early in experimental pancreatitis would modify the course of the disease.

METHODS

Adult mongrel dogs were used in these experiments. Under nembutal anesthesia (30 mgm. per kgm.) the duodenum was delivered, incised, and the accessory pancreatic duct located and cannulated. Eight to 10 cubic centimeters of bile aspirated from the animal's gallbladder were injected with maximum hand force, and the pancreas was observed to become discolored. The duodenum and abdomen were closed and the animals received no treatment other than that to be described. The first 24 dogs were operated upon in pairs, and the spin of a coin after both operations were completed decided which of the pair should be treated. The animal to be treated was then transfused with dog plasma in the amount of 25 cubic centimeters per kilogram of body weight. All dogs which died were autopsied, and the surviving animals were sacrificed and autopsied after 6 to 14 days.

The second group of experiments concerned crossing the circulation of a dog with early induced pancreatitis and a normal dog. The femoral artery of each dog was connected by a polyvinyl cannula to the femoral vein of the other, and the cross circulation was allowed to proceed for from 30 to 40 minutes. Both dogs received 1.5 milligrams per kilogram body weight of heparin.

RESULTS

Pancreatitis treated by plasma transfusion. Twelve dogs were treated by plasma transfusion and 7 died within the first 36 hours (58 per cent mortality). In the untreated control group of 12 dogs all but 2 died within 36 hours (83 per cent mortality). In all dogs dying of pancreatitis, autopsy showed hemorrhagic necrosis of the body of the pancreas (the descending process usually escaped) with varying extent of hemor-

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rhages and fat necrosis in the peritoneal cavity and on two occasions in the mediastinum. Histologically the changes in the pancreas were typical of hemorrhagic necrosis, and no foci of necrosis were found in the heart muscle or skeletal muscle of the diaphragm.

Pancreatitis treated by cross circulation. The effectiveness of cross circulation.—In 3 pairs of dogs Evans blue dye injected intravenously in 1 dog was found to be equally distributed between the 2 dogs within 15 to 20 minutes after the beginning of cross circulation.

The changes in blood volume between the 2 dogs being cross circulated.—On three occasions the blood volume of the normal dog was estimated by Evans blue dye dilution before and after cross circulation. In all three instances the volume fell, by 130, 240, and 390 cubic centimeters. In other words, the animal with pancreatitis was receiving a fairly massive blood transfusion (13 to 25 c.c. per kgm. of body weight).

Mortality of pancreatitis treated by cross circulation.—Twelve dogs were treated by cross circulation and 7 died (mortality of 58 per cent).

Changes in the normal dog.—Records were made of electrocardiograms and blood pressure of each dog. The electrocardiographic changes in acute pancreatitis are described elsewhere (Pollock and Bertrand, in press). In the normal dog in each pair there was, as a rule, no striking change in either the electrocardiogram or the blood pressure as a result of the cross circulation, but in a solitary normal dog, cross circulated with a dog which showed T wave inversion after induction of pancreatitis, a striking upright peaking of T in leads 2 and 3 was seen after 30 minutes of cross circulation. This was not accompanied by any marked change in blood pressure and persisted for 30 minutes after the end of the cross circulation.

No normal dog died as a result of being cross circulated with a dog which had pancreatitis.

DISCUSSION

Whatever the etiology of the pancreatic lesions of acute hemorrhagic pancreatitis may be, it is probable that the intraperitoneal lesions of hemorrhage, effusion, and fat necrosis are the result of liberation into the peritoneal cavity, by what amounts to a major rupture of the pancreas, of large quantities of activated pancreatic juice.

Hildebrand suggested that the hemorrhage so often associated with acute pancreatitis was the result of tryptic action. Rich and Duff produced lesions comprising medial hyalinization and necrosis, characteristic of those found in the pancreas in acute hemorrhagic pancreatitis by subcutaneous injection of crude trypsin, crystalline trypsin, and pancreatic juice. It has repeatedly been shown that the intravenous injection of trypsin renders the blood incoagulable by destruction of fibrinogen. Intravenous injection of trypsin causes profound shock and death in dogs and other animals.

It has been supposed that the shock, hemorrhage, and toxemia of early acute hemorrhagic pancreatitis are related to the presence in the peritoneal fluid and blood of increased amounts of proteolytic enzyme, although in fact all the pancreatic enzymes are found in increased amounts in the blood, and estimation of amylase has long been the standard diagnostic test for acute pancreatitis. Whipple and Goodpasture showed that pancreatic enzymes are rapidly neutralized in the peritoneal cavity and that the exudate 24 to 48 hours after production of acute hemorrhagic pancreatitis is nontoxic when injected intraperitoneally in other dogs.

In an attempt to overcome the "trypsin poisoning" which is supposed to contribute to the early deaths, interest has centered on the antitryptic substances, particularly soybean, sodium formaldehyde sulfoxylate, and plasma or serum, in which the antitryptic activity is concentrated in the albumin fraction.

Rush and Cliffton produced acute pancreatitis in 3 dogs by injection of bile into

the accessory pancreatic duct and treated them with a partially purified soybean trypsin inhibitor prepared by the method of Kunitz. All 3 dogs died, but the authors found some counteraction of shock and elevated proteolytic activity.

Coffee, Brinig, and Gillespie thought that crystalline soybean trypsin inhibitor protected small animals against the toxic effects of trypsin and modified the course of experimental pancreatitis.

Noskin, Popper, and Necheles produced, in 80 per cent of dogs, fatal peritoneal lesions like those found in acute pancreatitis (notably disseminated fat necrosis) by exposing freely in the peritoneal cavity a cuff of duodenal wall including the accessory pancreatic duct. After this maneuver 19 dogs were treated with crystalline soybean trypsin inhibitor intraperitoneally. Nine of them survived and when sacrificed showed no fat necrosis. The decrease in mortality from 80 to 53 per cent was not, however, statistically significant. Popper and Necheles later tested a number of antitryptic substances including detergents, sodium formaldehyde sulfoxylate, acridine 36, and cysteine hydrochloride, for their power to prevent fat necrosis in dogs prepared in the manner described, and found only sodium formaldehyde sulfoxylate effective when injected intraperitoneally. Of 13 dogs treated with various doses of sodium formaldehyde sulfoxylate by 1 to 5 intraperitoneal injections, 8 showed no fat necrosis when they died or were sacrificed.

Hoffman, Jacobs, and Freedlander treated 58 dogs with experimental acute pancreatitis with various doses of crystalline soybean trypsin inhibitor intravenously and 3 with the same intraperitoneally. They found no effect on the serum enzymes or the mortality rate.

Serum antitrypsin. The antitryptic activity of blood serum was first reported by Hildebrandt in 1893, and his observations were extended by Landsteiner, who found that the activity was concentrated in the albumin fraction of the serum.

Whipple and Goodpasture injected 20 to 90 cubic centimeters of dog serum daily intraperitoneally in a dog with severe induced pancreatitis. The dog died, and they found no benefit from the injections.

The first report of the use of concentrated serum albumin in this connection was by Kenwell and Wels. They treated 11 cases in humans of acute pancreatitis confirmed by operation with 300 to 500 cubic centimeters of concentrated albumin daily for from 3 to 5 days. None of their patients died, and they gained the impression of a more benign clinical course. They also treated 2 dogs with experimental acute pancreatitis and both dogs recovered. They concluded that the benefit seen in their patients was related to the antitryptic activity of the albumin concentrate.

Recently, Zollinger (quoted by Mackenzie) and Elliott working in Zollinger's department have thrown doubt on the idea that the benefit from the administration of serum albumin which they were able to reproduce to some extent in dogs, was related to its antitryptic activity. Instead, they found a profound fall in plasma volume which could be corrected by the administration of sufficient serum albumin with survival of the animal and without evidence of trypsin inhibition.

CONCLUSIONS

The decline in mortality in the present series from 83 per cent for controls to 58 per cent in dogs treated by either plasma transfusion or cross circulation is not statistically significant, (difference is less than twice the standard error of the difference). The results are sufficient to show, however, that the administration of plasma or allowing the antitryptic activity of the whole of a normal dog's blood to combat plasma trypsin in the pancreatic dog has no more than a partial effect in the reduction of mortality in acute pancreatitis. There was no evidence in any except 1 of the normal cross circulated animals of any toxic product carried over from the dog with pan-

creatitis. In this lone exception, a striking peaking of *T* in leads 2 and 3 of electrocardiogram was found after cross circulation.

SUMMARY

1. The administration of plasma soon after the experimental production of acute pancreatitis lowered the mortality from 83 to 58 per cent.

2. Cross circulation with a normal dog had the same result.

3. The significance of these facts is discussed.

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THE SERUM PROTEINS AND LIPOPROTEINS IN PATIENTS WITH CARCINOMA AND IN SUBJECTS FREE OF RECURRENCE

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THE PURPOSE OF THE PRESENT WORK was to investigate the effects of progression of disseminated malignancy by the measurement of the serum proteins and serum lipoproteins of the affected host, and to compare similar measurements in the serum of postoperative subjects free of cancer for prolonged periods.

The phenomenon of remission, either spontaneously or associated with the administration of bacterial products and the slow rate of growth of some malignant lesions, demonstrated by the survival of patients for 5 or more years without treatment, attests to the existence of a defense mechanism within the affected host. The presence of residual tumor in the operative field has been amply demonstrated after the most radical operation. This observation is further substantiated by the frequency of local recurrence of the primary tumor in the operative site after prolonged periods. Obviously, a better understanding of the host biochemical factors responsible for the restraint of residual tumor cells would probably contribute much to the means of controlling malignant disease in man and perhaps also lead to new facts concerning the etiology.

Previous investigators have demonstrated the association of abnormal serum protein and lipoprotein patterns in the blood of patients affected with malignant disease. The present work consists of a continuation of similar studies. In August of 1954, this study was initiated and the method of electrophoresis was employed as a means of following the response of the human host during the natural course of the disease and after surgical excision of the primary tumor.

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Dr. Lowell Erf, now deceased.

METHODS

Approximately 5 cubic centimeters of blood were obtained from subjects by venipuncture and transferred to a dry test tube. Sufficient time was provided for the clot to form. The serum was obtained by centrifugation. Filter paper zone electrophoresis of the serum was carried out, using a modified Grassmann apparatus containing veronal buffer (p_H 8.60, ionic strength .03). The supporting medium was Whatman No. 1 filter paper strips measuring 3.8 by 30.5 centimeters. Exactly .01 milliliter of serum was applied in a transverse band from a calibrated capillary pipette. Electrophoresis was carried out for 12 hours at 15 degrees C. using a potential difference of 150 volts and a current of .0004 ampere per centimeter. The strips were then removed from the electrophoresis chamber and rapidly dried at 100 degrees C. Each strip was then cut longitudinally into two equal parallel strips. One of the strips was stained for proteins with bromphenol blue, the other was stained for lipoproteins with Sudan III.

Strips stained with bromphenol blue were scanned at 620 millimicrons and strips stained with Sudan III were scanned at 560 millimicrons. Quantitative measurements of color intensity were continuously made and recorded by optical scanning. The relative proportions of serum protein components were then determined by measuring the area beneath the respective curves with a planimeter. Total circulating quantities of protein

TABLE I.—CONTROL DATA FROM 30 SUBJECTS

		SERUM PROTEINS, PER CENT			
	Albumin	*Globulins*			
		Alpha$_1$	*Alpha*$_2$	*Beta*	*Gamma*
Range	42.7–61.2	3.0–5.4	7.3–12.9	15.9–28.7	10.6–21.0
Average	51.1	4.0	8.6	18.6	17.4

	SERUM LIPOPROTEINS, PER CENT	
	Alpha	*Beta*
Range	12.5–42.7	57.3–87.5
Average	24.4	75.6

TABLE III.—CARCINOMA OF BREAST IN 14 CASES

		SERUM PROTEINS, PER CENT			
	Albumin	*Globulins*			
		Alpha$_1$	*Alpha*$_2$	*Beta*	*Gamma*
Range	30.6–47.0	2.1– 7.4	7.9–25.2	12.2–25.4	17.1–29.5
Average	38.7	5.4	14.4	19.3	21.8

	SERUM LIPOPROTEINS, PER CENT	
	Alpha	*Beta*
Range	0–24.1	75.9–100
Average	7.6	92.4

and lipoprotein were not determined in this study.

OBSERVATIONS

Control cases. Blood samples were obtained from 30 subjects presenting themselves at the blood donor center for blood donation and known to be free of disease. The serum protein findings (Table I) are in agreement with those previously reported for normal sera by Longsworth and Reiner and their associates. The serum lipoprotein findings by this method likewise are in agreement with the results of Durrum and Rosenberg and their coworkers. Two distinct sudanophilic zones were seen in the lipid electrophoretogram. The first peak (zone I) was seen in the region of the beta globulin and frequently consisted of 2 well differentiated components. This area was approximately 75 per cent of the entire sudanophilic area. The first component consisted of a smooth rise extending from the point of origin and leading into a more distinct and taller second rise in the region of the beta globulin. The first portion of this area is known to consist of neutral fat, while the second portion consists of cholesterol and phospholipids. The second peak (zone II) was seen in the region of the A_1 globulin and appeared to contain two components. The sudanophilic substance in this location consists of phospholipids and a small proportion of cholesterol. The relative proportion of lipid in zone II (alpha lipoprotein) was found to average 24.4 per cent. In 4 instances, values less than 20 per cent were noted. A value greater than 30 per cent was noted in only 1 instance.

Findings in patients with advanced and progressing carcinoma. The primary tumor involved the gastrointestinal tract in 10 male and female patients and the breast in 14 female patients. Two of the 24 patients studied were terminal; one patient had disseminated gastric carcinoma while the other patient had disseminated breast carcinoma.

The abnormal serum protein findings are shown in Tables II and III. All patients showed a hypoalbuminemia and a hyperglobulinemia. The greatest changes were noted in the albumin and alpha globulin fractions of the serum. The data accumulated by serial measurements show a continued fall in albumin concentration and an increase in the alpha globulins, especially the alpha$_2$ globulins, with progression of the neoplastic process. Terminally the gamma globulin has been noted to decline in a few instances. The reason for this phenomenon is not known. The serum protein findings, as

TABLE II.—CARCINOMA OF ALIMENTARY TRACT IN 10 CASES

		SERUM PROTEINS, PER CENT			
	Albumin	*Globulins*			
		Alpha$_1$	*Alpha*$_2$	*Beta*	*Gamma*
Range	29.2–46.3	6.7–12.1	10.4–19.3	14.1–23.2	14.1–24.7
Average	37.5	8.5	14.0	20.2	19.8

	SERUM LIPOPROTEINS, PER CENT	
	Alpha	*Beta*
Range	15.2–19.4	80.5–85.7
Average	17.0	82.8

TABLE IV.—"CURED" OF BREAST CARCINOMA FROM 3 TO 30 YEARS (8 CASES)

		SERUM PROTEINS, PER CENT			
	Albumin	*Globulins*			
		Alpha$_1$	*Alpha*$_2$	*Beta*	*Gamma*
Range	45.1–60.6	1.9– 4.5	5.5–12.5	17.4–19.9	10.1–25.9
Average	51.5	3.1	7.7	18.6	19.4

	SERUM LIPOPROTEINS, PER CENT	
	Alpha	*Beta*
Range	33.3–59.2	46.8–66.7
Average	42.6	58.1

can be seen, were similar in both types of carcinoma.

The most significant findings have been observed in the lipoprotein electrophoretograms of patients with carcinoma. A significant decrease in the proportion of alpha lipoprotein has been consistently observed in patients with progressing carcinoma. In the 1 instance in which the alpha lipoprotein approached normal proportion, the breast lesion was not associated with demonstrable metastasis at operation. In the remaining cases, abnormally low values were observed. Of the two types of carcinomas, the lowest values for alpha lipoprotein were noted in breast carcinoma. In 3 cases of breast carcinoma, alpha lipoprotein could not be detected. Cases of gastrointestinal carcinoma showed detectable, though low proportions of alpha lipoprotein. The absence of lipoprotein did not appear to be associated with poor nutritional status since in most instances, including cases with absent lipoproteins, the nutritional status appeared to be good and emaciation had not occurred.

Changes were also noted in the beta lipoprotein proportion and configuration in the serum. An increase in the proportion of beta lipoprotein was observed in cases of dissemination. Frequently, an abnormally large, distinct beta lipoprotein component with unusual mobility was observed. This was seen in cases with multiple metastasis, especially when the skeletal system was known to be involved.

Findings in patients "cured" of carcinoma. Eight patients free of clinical evidence of recurrence for at least 3 years and as long as 30 years after radical mastectomy for carcinoma were studied. The serum electrophoretogram in each case showed normal proportion of serum components (Table IV). The concentrations of A_1 and A_2 globulin were slightly less than control values.

The lipid electrophoretogram showed a significantly greater than normal proportion of alpha lipoproteins. In addition, the lipoprotein pattern was the same as that seen in normal serum. The beta lipid zone

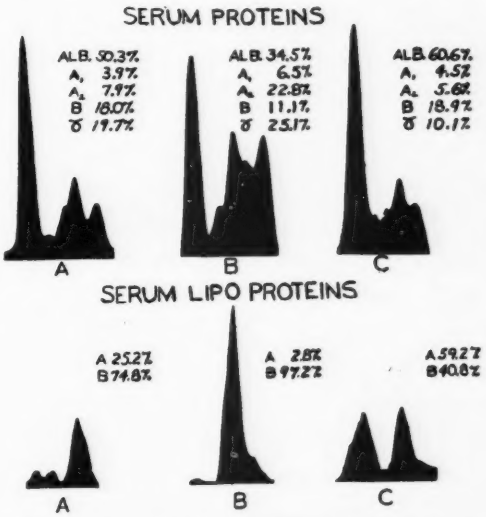

FIG. 1. Comparison of electrophoretic patterns of serum lipoproteins and proteins. A, Normal serum. B, Serum of patient with metastatic breast carcinoma. C, Serum of patient 5 years after radical mastectomy for breast carcinoma.

was likewise normal in appearance. The dense component of the beta lipoprotein seen in patients with dissemination and osseous metastasis was not present in this group.

DISCUSSION

Fruend and Kaminer in 1910 demonstrated that the blood serum of normal human subjects contained a carcinolytic factor capable of destroying human carcinoma cells in vitro. No such effect could be obtained with the blood serum of the patient from whom the tumor has been removed or with the serum of other patients with carcinoma. They found that the carcinolytic property of normal serum could be destroyed by heating, or by the addition of a small amount of serum from the blood of a patient with carcinoma. These investigators were able to isolate the active component from the serum. The substance was found to be a fat and associated with the albumin fraction of the serum.

The presence of a naturally occurring carcinolytic factor in the serum of the guinea

pig was demonstrated by Kidd. Remissions of transplanted lymphosarcoma of mice could be induced by treating the affected animal with normal guinea pig serum. The active principle of the serum was again found to be present in the end fragments of the serum when separated electrophoretically. Normal human serum had some effect and normal rat serum was incapable of producing the same effect on the transplanted mouse lymphosarcoma.

The inherent defense potential of the host was again demonstrated by Abderhalden in 1922. Human blood serum was shown to be capable of digesting a substrate consisting of protein which previously had interacted with the host. He postulated that this effect was due to the development of an *Abvehrfermente* (defense enzyme). On the basis of this phenomena, Abderhalden developed a test for pregnancy in which the blood serum of a pregnant woman was shown to be capable of digesting a substrate consisting of human placenta. Since the growth of the placental cells is somewhat similar to the invasion of neoplastic cells, these studies seem to be significant in regard to human neoplasia.

The observation that culture medium containing adult plasma would not support the growth of human mammary carcinoma cells in vitro suggested to Coman the possibility that normal adult serum contains an inhibitor or is lacking in some essential nutrient necessary for the growth of malignant cells in vitro.

Mider showed that a deficiency develops in the host during the growth period of a malignant tumor. The effects of tumor growth upon the host, namely, weight loss, anorexia, and nausea, could be ameliorated by feeding the tumor-bearing animal fresh carcinoma tissue of the same kind as that present in the affected animal. The animals began to eat better, gained weight, the growth rate of the tumor was comparatively lessened, and the animal's life was prolonged. A similar deficiency may occur in human cancer patients. The relative increase in this "deficiency" with rapid cellular growth, may explain the increasing anaplasticity observed clinically with progressive disease. Likewise, the basic deficiency may conceivably explain the inability to maintain a state of remission in human carcinoma patients, particularly when such states have been produced by cytotoxic agents or hormones.

Disturbed lipoprotein metabolism occurs in cirrhosis, nephrosis, atheromatosis, and carcinoma. Barclay has recently demonstrated, by chemical separations and ultra centrifuge studies, a significant deficiency in the alpha lipoprotein levels and an increase in the S_f 11-20 and S_f 21-100 beta lipoprotein levels in the serum of patients with advanced mammary carcinoma. The abnormal proportions of beta lipoproteins were thought to be associated with metastatic phenomena. The dense bands observed by electrophoretic separation in the serum of patients studied in this laboratory may be the result of increased amounts of these beta lipoproteins.

The sex hormones have been shown by Russ and associates to profoundly affect the distribution of lipoproteins in the serum. A decrease in alpha lipoprotein and an increase in certain beta lipoprotein components have been demonstrated in atherosclerosis. The administration of estrogens produces a reversal of the abnormal pattern; namely, an increase in the alpha lipoprotein and a decrease in the abnormal beta lipoprotein proportion. Androgens produce accentuation of the serum lipoprotein findings in atherosclerosis. The favorable effects of estrogen therapy observed in this laboratory in advanced prostatic carcinoma have been found to be associated with the restitution to normal of the lipid electrophoretogram, namely, a decrease in the proportion of beta lipoprotein and an increase in the alpha lipoprotein.

The naturally occurring phospholipids have been shown to exert a significant inhibitory effect on some of the known carcinogens. Dickens showed that the carcinogenic effect of benzpyrene in experimental

animals could be profoundly inhibited when the carcinogen was dissolved in solvents containing phospholipids. When a vegetable solvent such as sesame oil, which does not contain phospholipid, was used as a vehicle for 3-4 benzpyrene, 90 per cent of animals receiving the solution intramuscularly, developed malignant tumors. On the other hand, when ox brain lipid which contains phospholipid was used, the tumor incidence was reduced to 5 per cent.

Since the conversion of beta lipoprotein to alpha lipoprotein is known to involve the co-protein factor, clearing factor, and heparin, an investigation of lipoprotein metabolism in patients with carcinoma might be of value. The presence of large proportions of alpha lipoprotein in the serum of "cured" subjects, and low levels of alpha lipoprotein in patients with disseminated malignant disease, may conceivably be significant in relation to the control of malignancy by the human host. Clinical trials of replacement therapy in cancer patients with normal alpha lipoprotein from pooled human serum are in progress.

SUMMARY

1. The proportion of alpha lipoprotein to beta lipoprotein in the serum of 24 subjects with either advanced carcinoma of the breast or alimentary tract is lower than that observed in normal human blood donors.

2. A hyperglobulinemia and hypoalbuminemia are consistently observed in patients with active malignant disease.

3. The changes in both serum proteins and serum lipoproteins are accentuated with progression of the malignant process. In 3 cases of far advanced breast carcinoma, alpha lipoprotein was not detectable in the serum.

4. Eight subjects free of recurrence for prolonged periods, after successful surgical removal of a breast carcinoma by radical mastectomy, showed normal plasma protein patterns and greater than normal proportions of the alpha lipoproteins in their serum. The proportion and configuration of the beta lipoproteins were the same as those observed in normal serum.

5. In comparison with normal blood serum, the serum of subjects free of recurrence of carcinoma, after surgical removal of the primary lesion, contains a greater than normal proportion of alpha lipoprotein. This is interpreted as significant with regard to tumor-host relations.

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EDITORIALS

SUPRARADICAL OPERATIONS FOR CANCER

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IMPROVEMENTS in the art and science of surgery have led to a great widening of the surgeon's horizon. Operations regarded as surgical feats a decade ago have now become commonplace, owing in large part to the greater safety now possible in carrying out operative procedures. In the development of bigger and better operations, no group has been more energetic than those who have attempted to improve the treatment and cure of cancer. In an effort to widen the scope and better the rate of cure, operations formerly reserved for far advanced lesions have been adopted as routine procedures for early cancer, extensions of previous routine resections have been developed, and new operations have been devised. The term supraradical surgery has been coined to describe this new trend in the treatment of malignant disease. Some of the operations which might be included in this category are quarterectomy, routine total gastrectomy, so-called radical total gastrectomy, subtotal or total colectomy for localized cancer of the colon, pelvic exenteration, resection of solitary hepatic metastasis, and mediastinal node resection for cancer of the thyroid and certain cancers of the breast.

The value of all these procedures has been reported enthusiastically in a number of papers, and there is no question but that these new developments have indeed led to the cure of certain cases of cancer otherwise incurable. It is, nevertheless, advisable from time to time for surgeons to subject their experience to critical reappraisal in order to determine the value or limitations of current surgical procedure. It is possible for anyone who reviews his own experience in surgery to recall that some operations about which he was enthusiastic 10 to 15 years ago may now have been abandoned completely. In the case of supraradical surgery of cancer, it seems that evaluation should be directed to three items: (1) mortality rate; (2) disability, morbidity, or disfigurement of the patient; and (3) rate of cure.

What is the mortality rate for this type of surgery as compared to that obtaining in the standard classical operations? It is impossible to arrive at an accurate figure. Reports of a large series of cases presented by an individual surgeon or group have shown that the mortality rate can be kept as low as, or nearly as low as, that for less extensive operations. These reports are usually made by highly specialized surgeons who are developing a new operation or are especially interested in this field. There is reason to doubt, however, that this same low rate is being achieved by the average well trained surgeon who tries to emulate these specialists. A surgeon who attempts such new operations and finds that his own mortality rate has risen 5, 10, or 20 per cent above that which he previously experienced is not likely to announce this fact publicly. If one compares published mortality rates for total gastric resection with those for subtotal gastrectomy he sees that the rate is appreciably greater for total resection. This does

not mean that the operation is not a useful and valuable one, but it does imply that until or unless surgical skill throughout the nation reaches higher standards than obtain at present the operation can hardly be regarded as the method to be used routinely by all surgeons. Teachers of surgery should bend every effort to train the oncoming generation so that the average surgeon of the next decade will approximate the skill and judgment of the leaders of today. If that is attained, then supraradical surgery may be practical in every community and with a suitably low mortality rate. There inevitably will come a time, however, when the law of diminishing returns will limit the extent of further surgical ablation of tissues.

Regarding the second question of morbidity, deformity, or disability of the patient following supraradical operations, there is considerable difference of opinion among both surgeons and patients. Most of them would like to eat their cake and have it too. The patient, particularly, does not want a disability or deformity, but he does wish to be cured. The surgeon here needs to take the initiative. The patient is a layman who will in all probability be guided by the surgeon's advice, and the latter can "sell him" or discourage him from a given course. The surgeon should not take advantage of his knowledge to convince the patient that a big operation is better for him than a less extensive one unless there is clear-cut evidence of the superiority of one operation over another. Patients who become partial outcasts because of disfigurement, invalids because of loss of extremities or inability to eat or properly digest food, or who suffer long periods of disability before they finally can resume more or less normal activities may ultimately feel that they have paid a high price for the privilege of living unhappily. Different procedures each present different hazards and challenges. Not infrequently, of course, the operation may change an apparently hopeless cripple into a self-respecting and useful member of society, but surgeons must remember that the opposite effect may also occur and must therefore exercise their most mature and careful judgment based on well documented evidence. On the whole, while it is recognized that morbidity and crippling of one sort or another may follow these extensive operations, in many instances it is not too serious a problem.

Finally, and probably most important, is the question of improvement in rate of cure of cancer. It seems self-evident that if a given cancer would be cured by a limited operation, it would also be cured by a more extensive one, provided the patient survived. One would, therefore, expect the rate of cure certainly to be as great, but one would be justified in continuing the more radical resection only if a significantly better cure rate could be clearly demonstrated. In the case of most of the supraradical procedures at present advocated, there has been insufficient time since their introduction for enough data to have been collected and evaluated. Surgeons used to speak of 5 year cures of cancer of the breast, but it is now well recognized that widespread recurrence or distant metastases may appear 7, 8, 9, or 10 years after operation and apparent cure. While most other common cancers seldom lie quiescent for as long a time, it is well recognized that evaluation is extremely difficult. It takes many years to arrive at a final and unequivocal answer. At the present time, it seems fair to state that significantly better results have not as yet been established. This fact does not mean that such operations should be abandoned, but it does mean that a surgeon is not standing in a completely defensible position when he asserts positively that he can accomplish more by a bigger operation. Any surgeon who has progressed in the treatment of cancer beyond the stage in which he carries out a given procedure only because he has been taught to do it that way recognizes the vagaries and variability of this disease or group of diseases. He sees one patient cured by an apparently inadequate operation, and another not cured by the most radical

type of procedure. The difference in the biologic nature of cancer, and the host's reaction to it, may give rise to the disquieting thought that these factors may be more important than the nature and extent of the surgical attack. Some surgeons hold to the belief that supraradical operations are never indicated, that if the patient cannot be cured by what has previously been regarded as adequate he will probably also not be cured by a vastly wider excision. It is obvious that the problem is not yet solved, but still needs intelligent and skillful study.

At the present time, it would seem that supraradical surgery should be carried on by those surgeons who are particularly well qualified and who have adequate facilities for its performance. For the average well trained surgeon, the operation for cancer should be adjusted to the apparent needs of the individual patient and should be the one which gives hope of cure, with as little deformity or disability as is consistent with such hope, and which is not attended by a prohibitively high mortality rate. It is the surgeon's obligation not to carry out bigger and better operations in order to enhance his own self-esteem or his professional standing by being able to publish a large series of successful massive resections when as a matter of fact equally good results with considerably less patient disability could have been achieved by present standard radical procedures.

CHOLEDOCHOTOMY

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THAT THE TECHNIQUE OF EXPLORATION of the common bile duct is not standardized, and often extremely unsatisfactory, has been attested by numerous clinical reports and by a rising wave of interest in operative cholangiography. As a recent example, Hicken, McAllister, and Call have shown by postoperative cholangiograms that 20 per cent of a series of 110 patients who had had operations for stones in the biliary tree had retained stones in the common duct 10 days later. That this was a serious complication was proved by the fact that 81 per cent of these patients later required secondary explorations.

Obviously, any method that will aid in a reduction of the incidence of retained common duct stones, variously estimated by Johnston, Waugh, and Good as from 2 to 26 per cent, should be investigated, and, for this reason, operative cholangiography has offered great promise. But, before the surgeon transfers a portion of the responsibility for such errors to the radiologist, he had better first study his own technique of exploration of the extrahepatic biliary tree.

Assuming that the surgeon has opened the common duct with the expectation that stones will be found, and already has removed as many stones as possible with stone forceps or scoops, there are still three common errors that must be corrected before an exploration can be considered to be adequate. By far the most important is the exploration of the lower end of the duct. Many surgeons have been reluctant to force probes or dilators through the ampulla, and therefore never are able to tell whether or not there is an actual ampullary obstruction. It would be as illogical to do a laparotomy for intestinal obstruction without a rectal examination as to open a common duct without a thorough investigation of the functional patency of the sphincter of Oddi. Furthermore, the value of ampullary dilatation has been proved repeatedly and it has been demonstrated that stones left in the biliary tree can pass postoperatively through a dilated ampulla. Thus, Allen and Wallace, in a previous study from this hospital, showed that secondary operations for stone were required in 4.21 per cent of 214 patients who had no ampullary dilatation but in only 0.71 per cent of 561 who had a dilatation performed.

The only real argument concerns the method by which dilatation of the sphincter of Oddi should be accomplished. In essence, if it cannot be effected easily or satisfactorily by instrumentation through the duct, a transduodenal exploration is essential. If a surgeon uses Bakés' dilators, he must assure himself that they have actually passed into the duodenum and not merely invaginated the papilla. He must dilate the ampulla preferably to a diameter 1 millimeter less than that of the duct and finally prove that it is patent by saline irrigations.

The second common error involves the cystic duct remnant. Except when a long cystic duct parallels the common bile duct behind the duodenum, it is essential to leave only a short remnant of the cystic duct but to avoid amputation flush with the common duct wall. Perhaps even more important is the necessity of probing the cystic duct carefully, preferably in a retrograde fashion, to be certain that no small calculus is left within its lumen.

The final area that often merits more careful exploration is the intrahepatic duct system. If the hepatic ducts are calibrated

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by dilators and the sphincter of Oddi is dilated to a significantly wider diameter, it is probable that any stones higher in the hepatic ducts should pass later through the ampulla.

It is important to determine whether or not application of these principles will result in a low incidence of retained common duct stones. This figure may be determined in two ways, either postoperative cholangiograms may be made or patients may be followed for a sufficiently long period to be sure that they are free of symptoms. Although occasional errors in interpretation of postoperative cholangiograms occur, it is generally agreed that this is the more satisfactory method since conclusions are based on objective rather than subjective evidence.

The author accordingly has reviewed 100 personal consecutive cases in which the described technique was followed, operative cholangiography was not used, and postoperative cholangiograms were done in all cases 7 to 10 days later. Stones had been found in some portion of the biliary system in all; in 53 cases they were present in the common duct. In only 1 instance—and here the operation was discontinued after an arduous transduodenal exploration with the full recognition of the fact that there was still a stone imbedded in the head of the pancreas—was there evidence of a retained stone. This patient has been free from symptoms referable to the biliary tree for the 2 years which have elapsed since operation.

These data suggest that a retained stone is a rarity when this technique is used. Though the comparable percentage error inherent in operative cholangiograms is difficult to determine, studies of available reports suggest that they are subject to erroneous interpretation more frequently. Thus, Mixter, Hermanson, and Segel did operative cholangiograms prior to indicated choledochotomy in 113 cases, with 5 false positive and 9 false negative reports.

The importance of operative cholangiography, particularly in secondary operations, should not be denied. However, it seems reasonable to conclude that the surgeon who wishes to reduce the number of retained stones can accomplish this purpose more effectively by first perfecting a sound surgical technique rather than by compromising with radiologic substitutes.

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THE SURGEON AT WORK

ACCURATE PLACEMENT OF THE PENROSE DRAIN

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POOLING OF URINE about the site of plastic repair in the renal pelvis, ureter, or bladder hinders good wound healing.[1] The trend, in urology at least, is away from splints and catheters. Good extraluminal drainage is, therefore, most important.

The method of tacking the tip of the Penrose drain in exact position with a plain catgut suture has been used, but this technique has the disadvantage that usually the catgut does not disintegrate sufficiently to release the drain, which can then only be withdrawn from the wound with a jerk.

A technique has been developed in the experimental laboratory which has proved effective in clinical use (Fig. 1). A catgut suture is stitched through the end of the Penrose drain, and tied. The needle on the long end is then passed through the tissue at the exact site from which drainage is desired (Fig. 1A) and is brought out of the wound alongside of the drain. Traction on the suture draws the end of the wick to the predetermined area. The two are clamped together in order to maintain the drain in position during the closure. Alternatively, the suture can be stitched through the drain outside of the wound and tied, to be cut subsequently, at the time of removal.

After closure of the incision, the suture is trimmed close to the skin, so that on removal no contaminated material will pass into the wound (Fig. 1B).

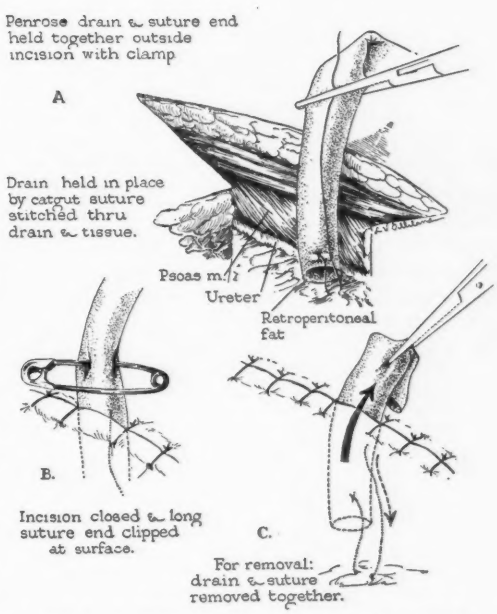
Penrose drain & suture end held together outside incision with clamp
A
Drain held in place by catgut suture stitched thru drain & tissue.
Psoas m.
Ureter
Retroperitoneal fat
B.
Incision closed & long suture end clipped at surface.
C.
For removal: drain & suture removed together.

FIG. 1. A, Catgut suture, tied to tip of Penrose drain, is passed through tissue at site to be drained and clamped to the drain outside the wound until closure is completed. B, Suture cut at surface of incision. C, Gradual withdrawal is permitted, since the suture trails after the drain.

Later, withdrawal of the drain can be gradual, since the suture will follow in reverse the course it took on placement (Fig. 1C).

SUMMARY

An easy technique is described for suturing a Penrose drain in place, yet allowing its ready withdrawal.

Supported by the James W. Edwards Fund for Medical Research.

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THE LATERAL DECUBITUS POSITION IN THE SURGERY OF CERVICAL ESOPHAGEAL DIVERTICULUM

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IN THE SURGICAL EXTIRPATION of an esophageal diverticulum, difficulty is usually encountered in two places: (1) the identification of the muscle cuff about the base of the diverticulum and (2) determination of the extent of removal of the redundant esophageal mucosa. With the patient lying in the supine position, it is necessary to rotate the head to the side (usually to the right, for most esophageal diverticula present on the left) in order to carry out the operative procedure. This rotation places the sternocleidomastoid muscle under stretch and hinders dissection, for one must constantly retract the muscle for exposure of the esophagus. In the supine position, to visualize the entire circumference of the base of the diverticulum it is necessary to rotate the esophagus through approximately 110 degrees by traction of the diverticulum. Thus the junction site between the esophageal mucosa and diverticulum is distorted, so that difficulty may be encountered when the decision is made as to the right amount to be removed or to be left remaining.

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By placing the patient in the lateral decubitus position, with a small pillow under the neck (Fig. 1), the sternocleidomastoid muscle is relaxed completely, and dissection necessary to reach the esophagus and diverticula is made much easier (Fig. 2). Very little traction is necessary on the muscle, on the underlying carotid sheath posteriorly, and the thyroid anteriorly. The diverticulum is easily viewed and dissected. The circumference of the base of the diverticulum comes readily into view, with little distortion, for the posterior and right rim of the muscular cuff can be quickly seen when the diverticulum is rotated only approximately 15 degrees. By placing the patient in the lateral decubitus position, the esophagus, for all practical purposes, has already been rotated 90 degrees from the horizontal so as to bring into view those portions which are usually seen with difficulty.

A large catheter (French No. 32) is then placed in the esophagus by the anesthetist, and when the dissection at the junction of the esophagus and diverticulum is complete and there is no undue distortion, the esophageal mucosa is incised and closed with interrupted No. 000 catgut

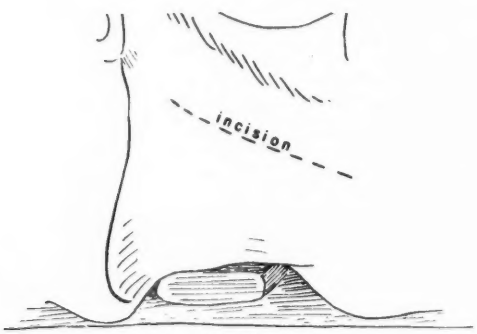


FIG. 1.

FIG. 1. The patient is placed in the left lateral decubitus position unless roentgenograms show presentation of diverticulum on the right side. A small pillow or folded towel is placed under the neck. The incision is made along the anterior border of sternomastoid muscle.

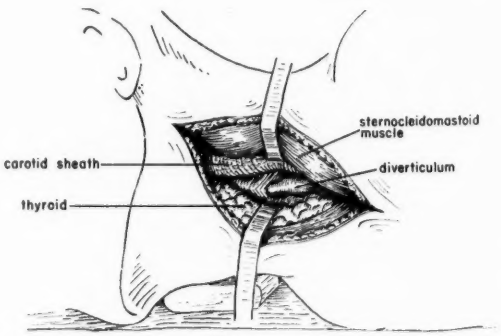


FIG. 2.

FIG. 2. Little retraction is needed to expose the diverticulum for the sternomastoid muscle is relaxed in this position.

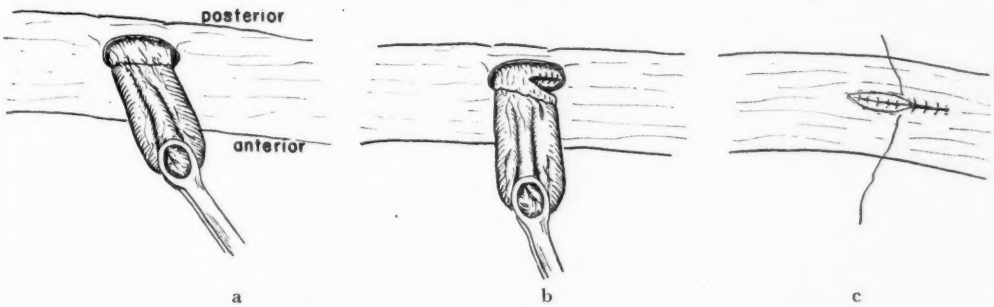


FIG. 3. a, The posterior and right edge of the junction of the esophagus and diverticulum is readily delivered with little rotation of the diverticulum and hence, little distortion of the junction site between mucosa of the diverticulum and esophagus. b, The mucosa is incised and sutured in stepwise fashion using traction on the diverticulum for better exposure. c, The muscular rim is sutured with interrupted No. 0000 silk. The larger the base of the diverticulum, the greater the advantage of the lateral decubitus position.

in a step-wise fashion (Fig. 3). The muscle cuff is then approximated with No. 0000 silk using the Lembert stitch. A small Penrose drain is left in place and brought out through the lower end of the incision. This drain is usually withdrawn in 48 hours.

The greater ease with which the entire circumference of the diverticulum base can be defined, when the patient is in the lateral decubitus position instead of the supine position, has been noteworthy, and is, therefore, being reported so that others may be encouraged to try it.

The Book Shelf

ON LISTERISM

SIR GORDON GORDON-TAYLOR, K.B.E., C.B., F.R.C.S., F.A.C.S.(Hon.), London, England

IT IS AN HONOR and a privilege to be afforded an opportunity of keeping ever green the memory of a great Englishman, Joseph Baron Lister, and of rendering, however imperfectly, a tribute to the illustrious shade of this modest Quaker surgeon who in his lifetime transformed the whole story of surgery. Such a commission, though pleasant, might well be deemed superfluous, but a century has passed since Lister's penchant and genius for investigation first had scope, and 43 years have rolled on since he died. The palimpsests of memory grow blurred and indistinct with time: it is easy to forget: in the words of the Roman poet, "Omnia fert aetas animum quoque."[1] Even the Saints themselves require their Saints' Days to "jog" the memories of sinful and forgetful mankind.

Perhaps my sole qualification for this present role is that I am possibly the only one in a distinguished surgical assembly, or at any rate one of the very few who beheld Lord Lister in the flesh. Exactly half a century ago, I occasionally saw him crossing the roadway from his house at 12 Park Crescent to the Regents Park Gardens. Age had already imposed her decree upon the human thrust, and the processes of ingravescent decay and decline already had him in their clutches; at that time he seemed a frail and aged figure, shorter in stature than he must have been in earlier life; he must then have been in his late seventies.

It behoves me to be brief, and I would beg of you to regard this contribution of mine rather in the nature of a "silent toast" such as we at the Royal College of Surgeons of England drink "to the immortal memory of John Hunter" at the biennial Hunterian Festival on February 14, and at our Buckston Brown Dinner in the same institution in Lincoln's Inn Fields in memory of a generous benefactor to our College, as well as at certain army reunions where those who have "passed on" are remembered for a few minutes in silent thought. This brief intrusion of mine is a sort of εὐφημία in the Platonic or Sophoclean sense, an invitation to "hush and be still," a lull for a few minutes before the busy hum of surgical contribution and controversy shall fill a great amphitheater and the future publication of learned communication tax the forbearance of sympathetic editors.

Remembrance is the greatest incentive and inspiration which history can offer to those who labor in like causes today. Let us remember for a moment this great scientist and surgeon.

The incorporation of a man's name, such as is Listerism, in the vocabulary of his own country or even in international parlance bespeaks the measure of his service to humanity—service which is perhaps God's greatest gift to man. Examples of such nomenclature come readily to mind: terms like Christianity, Buddhism, and Mohammedanism commemorate great leaders of religious thought, creed, and action. The contribution of the author or sponsor of some system of philosophy or a novel scientific principle or policy is re-echoed in terms such as Platonism, Marxism, Galvanism, and the like. The storehouse of such terms is indeed a rich one, including

From an Address delivered in Copenhagen, July 25, 1955.

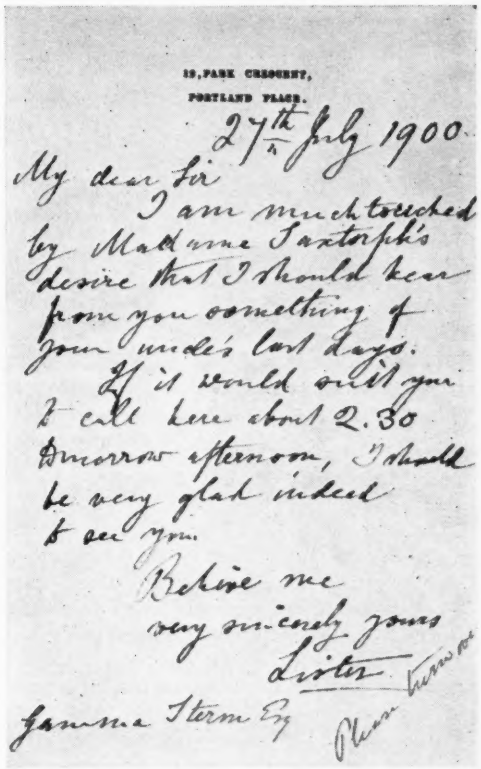
[1] "Time bears away all things, even the memory."

in its diversity scientific words like the ohm, volt, ampere or millicurie, the ill-omened guillotine, Baconian and Draconian in the jargon of history and law, and the slipshod nomenclature of operative techniques exhibited in a "Billroth I" or a "Bassini." Never has the coinage of our vocabulary been more nobly enriched than by the inclusion of this word Listerism, since in the words of Lord Moynihan: "If services to mankind are the standard of a man's greatness, Lister was the greatest that the world has known, first among material benefactors of mankind"; and again in one of the many addresses which the silver-tongued President of the Royal College of Surgeons of England of that era gave on the occasion of the Lister Centenary in 1927: "Nothing of which this world has knowledge has rescued so many lives, spared so much suffering, lifted so heavy a load of apprehension and sorrow from human hearts as has the work of this Quaker hero. For him I have justly proclaimed that he has saved more lives than all the wars of all the ages have thrown away."

This has been a year of centenaries of British surgeons—Bland-Sutton, Bowlby, D'Arcy Power; and the year 1955 is also the centenary of the real opening of the Edinburgh doors to the young Quaker surgeon from south of the Anglo-Scottish border. Lister had a memorable 1855: he obtained the Fellowship of the Royal College of Surgeons of Edinburgh in that year; he had secured the Fellowship of the younger English College 3 years previously, and though already an English Fellow he had been proud to be Syme's house surgeon till February 1855. In that same year he took rooms in Rutland Street opposite Syme's house and secured a classroom in 4 High School Yard where on November 7 he gave his first lecture on the "Principles and Practice of Surgery." Six weeks previously he had begun to work on the "Early Stages of Inflammation," studying the process with the microscope in frogs which he obtained from Duddingstone Loch on the outskirts of the Scottish capital. In 1855 also, he became affianced to Agnes, Syme's daughter, whom he married in 1856, the year in which he was appointed Assistant Surgeon to the Edinburgh Royal Infirmary.

> God's plans, like lilies pure and white, unfold
> Time will reveal the calyces of gold.

Who shall say that the young Edinburgh surgeon Mackenzie's death of cholera in the Crimea


19, PARK CRESCENT,
PORTLAND PLACE.

27th July 1900

My dear Sir

I am much touched by Madame Saxtorph's desire that I should hear from you something of your uncle's last days.

If it would suit you I call here about 2.30 tomorrow afternoon, I should be very glad indeed to see you.

Believe me
very sincerely yours
Lister

Fig. 1. Letter from Lord Lister to Professor Saxtorph's niece.

in the autumn of 1854 was a vain sacrifice? Scots have at all times hastened to join the colors when war menaces, and Mackenzie died as surgeon to a famous Scottish regiment, the 79th Cameron Highlanders. Half a century later the man who took his place at the Edinburgh Royal Infirmary was to be lauded and feted at a banquet given in his honor by the leading scientists of France, at which Lucas-Championnière proclaimed that Lister deserved the gold statue envisaged by Nélaton years before for him who should elucidate the cause of wound sepsis; and at the same banquet Pinard, the famous French gynecologist, said: "Lord Lister, you have driven back death itself; in all you have done, you have only caused tears of gratitude." In 1902, at the banquet of the Royal Society, Mr. Bayard, the United States Ambassador at the Court of St. James, addressing Lister, employed these few simple words: "My Lord, it is not a profession, it is not a nation, it is humanity itself which with un-

FIG. 2. Corner of church and operation room in Frederiks Hospital, Copenhagen. Lister's portrait on the wall.

covered head salutes you." God's will had been done. Mackenzie's death and sacrifice had not been in vain.

The reference to Lord Lister during a meeting of the Société Internationale de Chirurgie in Copenhagen is not inappropriate, since Lister 104 years ago held the post of house surgeon at University College Hospital, London, to Sir John Eric Erichsen, who himself was born in Copenhagen, the son of a Copenhagen banker belonging to a well known Danish family; and it was Erichsen who in 1897, nearly half a century later, made the presentation to his distinguished pupil of the Lorimer portrait of Lister which now hangs in the Library Hall of the University of Edinburgh.

Lister himself always averred that Professor Mathias Hieronimus Saxtorph (1822–1900), the chief surgeon of the Frederiks Hospital, Copenhagen, was the first of the surgical pilgrims from abroad who came to see the antiseptic method; this was in Glasgow in the summer of 1869. On the other hand, Valdemar Holmer (1833–1884) of the Kommune Hospitalet was said by Larsen and by Salomonsen to have been employing antiseptic methods as early as 1867; but Schaldemose in his lecture in 1917, the fiftieth anniversary of the commencement of Listerism and again in Lister's centenary year, 1927, maintained the priority of Saxtorph in Denmark. Saxtorph was not only the first, but a repeated visitor to Glasgow and Edinburgh, and on one occasion was accompanied by Dr. Engelsted and Dr. M. Christensen, grandfather of my friend, Dr. Djorup of Kolding, president of the Danish Surgical Society. The letter (Fig. 1) written in 1900 by Lister to Saxtorph's nephew confirms the endurance of the friendship between the two men, and if further confirmation were required, it is to be found in the portrait of Lister which hung in the room of the old Frederiks Hospital which served as church and operating room.[2] The portrait remained till the time of Oskar Bloch who was Saxtorph's successor and of Schaldemose and may be seen in the two illustrations (Figs. 2 and 3). One shows Bloch operating with Schaldemose as assistant; Johannes Ipsen, a former member of the Viking Surgical Club, is beside Bloch. Schaldemose, by that time Professor of Surgery, and Djorup, his first assistant, attended the Lister Centenary occasion in London in 1927. Madsen of Copenhagen had visited London in 1907 to pay homage to Lister on the latter's eightieth birthday.

The pioneer is rarely the exploiter, and the man who destroys an old edifice and marks out the lines of a new one does not often live to see the walls arise. In this respect Lister was fortunate, for he had been spared to see the seed which he planted survive the apathy and all the frost of hostility that threatened it; he had watched it bud and blossom and flower. He did not live to witness its full fruition, nor would he have wished this, for the horizon of the gospel which he preached for mankind is boundless, and his work opened to our gaze an unending vista for surgical advance. Epictetus, the Stoic philosopher, employed the term *τὸ ἡγεμονικόν* to indicate the master quality in a man; as with many of the great, so also with Lister *τὸ ἡγεμονικόν* was his incessant insatiable industry, coupled with a passionate search after truth and his infinite compassion. Throughout his life he had been a man with a mission which he pursued with as austere a devotion as any saint or prophet. Doubtless his Quaker background inculcated in him his meticulous accuracy in pursuit of truth: "to be slovenly in this search was not so much error as sin"; truth was to be sought earnestly, without passion, without prejudice; no trouble must be spared to ensure that the statement is trustworthy.

In science, fortune favors the mind that is prepared: whether Lister heard of Pasteur's work on the problem of fermentation at a dinner, as some affirm, or during a walk with Anderson,

[2]The old Frederiks Hospital is no longer a haven for the sick, but is now a Museum of National Industries. The Lister portrait is now in Professor Dahl-Iversen's room in the present hospital and in the same frame!

Professor of Chemistry in Glasgow, is immaterial; at any rate Lister was quick to realize that the biologic truths established by Pasteur might be applied to other circumstances and problems. In him the habit of observation and genius in experiment were happily combined, and truth slowly and surely emerged.

The story of Lister's life presents him as no exuberant, daimonic figure of fierce enthusiasms; yet what thrills must have been his as he saw the knots untied which had hidden the secrets and the gradual denouement of the problem to the solution of which he had devoted his genius —thrills akin to Keat's stout Cortez:

> . . . when with eagle eyes
> He stared at the Pacific—and all his men
> Looked at each other with a wild surmise—
> Silent, upon a peak in Darien

Or was it a more sober sense of self-satisfaction akin to that expressed in lines such as those penned in more recent years by Bernard Fergusson, the chronicler of that famous Scottish regiment, the 42nd, or Black Watch:

> The night braids up her darkness like a curtain,
> The morning star grows pale,
> Till suddenly the hope is sure and certain
> That death cannot prevail.

It would be wasteful of time in such a conference to give the lie to the suggestion that the antiseptic method with its lotions, sprays, and such devices was Lister's only creation, and that aseptic surgery was a separate discovery. Aseptic surgery was destined to follow on antiseptic surgery, as Lister himself had envisaged, as surely as daylight follows night, and Moynihan wrote: "Aseptic surgery is the reasoned practice of antiseptic surgery." The discovery of chemotherapy and the advent of the antibiotics have added to our secure and safe asepsis, while operating theaters are today cunningly caparisoned against air infection to which attention has turned once again after nearly 90 years.

I am indebted to Lord Webb-Johnson for the information that although the word antibiosis had first been employed in 1889 by Vuillemin and had received its blessing in 1899 from Marshall Ward in reference to microbial antagonism, as long ago as November 1871 Lister himself had noted under the microscope the retarding effect on bacterial motility of a growth of Penicillium glaucum. From the time of Pasteur and Lister, workers have been trying to kill one microbe with another—the idea was there, but

FIG. 3. Professor Oskar Bloch with Schaldemose operating in the operation room of the old Frederiks Hospital. Lister portrait on the wall.

fulfilment had to await the chance observation of Fleming, which was followed by the noteworthy work at Oxford and the Americas.

In the autumn of his lifespan honors came to Lister in profusion, "thick as the leaves that strew the brooks in Vallombrosa." They descended on him from the European continent where from the first surgeons had been quick to appraise, approve and apply, for a prophet is not without honor save in his own country. Reference has already been made to early Danish surgical pilgrimages to Scotland in the eighteen sixties, but perhaps the first and most loyal continental apostle of all was Just Marie Marcellin Lucas-Championnière along with his compatriots Terrier, Berger, and Périer. Yet in contrast to the general reluctance of France, despite the origin of Listerism from Pasteur's work, to accept and embrace the new principle, Germany was enthusiastic—Von Nussbaum of Munich, Volkmann of Halle, Thiersch of Leipzig, Bardeleben's assistant, A. W. Schultze, Theodor Kocher of Berne and Ernst von Bergmann, who soon was convinced that antisepticism was only a transition stage and that asepticism was the method of the future. The Italian and Iberian peninsulas were mostly apathetic, and distant America did not subscribe to the Tacitean adage "omne ignotum pro magnifico est."

At long last came recognition and in due course honors from doubting, hesitating Britain for this humble unspoiled man who, on receiving the Copley Medal of the Royal Society in 1902 at the age of 75, said that he had "often thought if ever he deserved credit, it was at the time when,

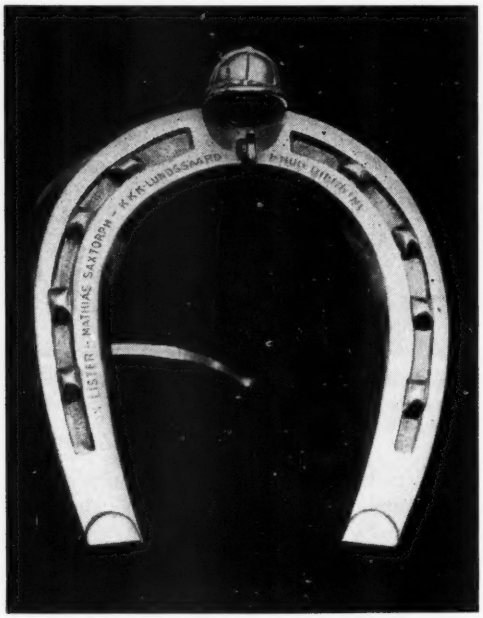


FIG. 4. This photograph is of a "watch holder" in the form of a horseshoe and was presented by Lord Lister to Professor Mathias Saxtorph who was a frequent visitor to Lord Lister's clinic and who was passionately fond of riding. In his last years Saxtorph presented it to K. K. K. Lundsgaard, Professor of Ophthalmology in the University of Copenhagen. The son of Professor Lundsgaard then gave it to Dr. Knud Bierring of Roskilde, a Danish surgeon, in whose possession it now remains.

perfectly convinced of the truth of the principle on which he acted and persuaded alone of the enormous importance to mankind of being able to carry that principle in practice, he worked for years with exceedingly little encouragement from his surgical brethren."

By the beginning of the century the winter of his life was at hand; in 1907 his eightieth birthday was celebrated all over the world: a Festschrift which continental custom associates with a seventieth birthday now belatedly made its appearance in the form of two volumes which contained all Lister's addresses and communications which he himself considered of permanent value. Vienna and Berlin paid him tributes; von Eiselsberg, subsequently to become a Lister medallist, spoke to a lantern slide of Lister; the German lay press hailed him as a "benefactor of humanity." Madsen of Copenhagen and Tilanus of Amsterdam made pilgrimages to London. But he was aging fast, both physically and mentally.

Although the Pyramids and the Taj Mahal still constitute an impressive memorial for Cheops and the Indian girl, Shakespeare well knew the brevity of marbles, and the spectacle of mouldering graveyards today and the changing face of nature and of town foretell with a melancholy prescience that in far distant centuries to come the material memorials of the man of whom we at this moment are thinking must inevitably crumble and be no more than Shelley's Ozymandias, king of kings, out in the desert where "boundless and bare the lone and level sands stretch far away." The portraits of Lister will disintegrate in the eons of futurity, the effigy of the modest Quaker surgeon which in his lifetime found a place in bas-relief on the tympanum of the façade of the Policlinico Umberto I in Rome will be no more, even the bronze monument by Sir Thomas Brock which today surveys from its height the southern vista of London's chief boulevard. Assuredly in the end there will disappear in the rubble the hospitals, institutions, and buildings that bear his honored name from Johannesburg to Sydney, from Britain to Auckland and Melbourne in the Southern Hemisphere.

The models which illustrate some of Lister's best known experiments set up in *piam memoriam* in the Department of Surgery of Edinburgh University by that distinguished surgeon, Sir James Learmonth, a Lister medallist, like Evarts Graham and Réné Leriche, will surely, alas! in days ahead disintegrate and dissolve. In the abysm of futurity perchance even the medical societies which today bear his honored name may transfer their allegiance to some other worker yet unknown. But the spirit of Lister will live on and his work and all that he stood for, *monumentum aere perennius*, like the poetic outpourings from Horace's felicitous pen. Far away across the North Sea, high up on the Castle Rock which guards the Scottish capital, stands the lovely shrine which commemorates in beautiful fashion those of Scotland who perished in the First Great War, "the war to end wars" (!); and in the shrine is an alcove dedicated to those who fell in the Royal Scottish Fusiliers, a Lowland regiment with which I have had a strong family connection, where are inscribed those wonderful lines which Thucydides, the great historian and master of Greek prose, puts in the lips of Pericles

in his famous funeral oration over the Athenian dead:

> The whole world is the tomb of great men. Neither is their name graven only on stone which covers their clay, but abideth everywhere without visible symbol, wrought in the stuff of other men's lives.

Wrought in the stuff of other men's lives! Our lives! And the lives of all who shall follow us in our profession. It was Lister who robbed and who will forever have robbed surgical operations of their terror and deadly peril, who cleansed the Augean stables which the hospitals resembled in pre-Listerian days, who ensured the safety of wound healing so that every scar is the caress of Lister's hand, and who has endowed the surgeon, wheresoever and whensoever he may practice his art, with a power unknown till Lister's day to restore health and keep death itself at bay.

And for a final picture of this man, let me finish with those lines written by Henley, himself a patient of Lister in the Edinburgh Royal Infirmary:

> His wise rare smile is sweet with certainties,
> And seems in all his patients to compel
> Such love and faith as failure cannot quell.
> We hold him for another Herakles,
> Battling with custom, prejudice, disease,
> As once the son of Zeus with Death and Hell.

Or perhaps I might borrow those words of the Roman poet whose memory some of us in Britain still cherish and celebrate his life and work each year; they seem to describe in 4 words the qualities of the man who was the inspiration and whose name finds commemoration in the name "Listerism": "Integer vitae scelerisque purus." What an epitaph!

Reviews of New Books

WRITTEN ORIGINALLY IN GREEK, the volume entitled *Gynecologie*[1] by N. C. Louros was translated into French and viewed by an English or rather American-thinking reviewer. All of these factors may have added to the dislike for this book by the latter who has diligently looked at all of the illustrations and read a portion of the text.

There are 397 figures, practically none of which is original with the author. He has been most catholic in his borrowing; the majority are from Martius, but also included are Stockel, Weibel, Ludwig, Dessin, and among American sources TeLinde, Huffman, Curtis, Novak, and the trade magazine *What's New*. Unfortunately, the reproductions are frequently very poor in quality. The reviewer was particularly depressed by comparing illustrations from Curtis-Huffman's textbook in the original and as reproduced in this book. Most of the illustrations are in black and white, but a few colored plates are included. There is no index and peculiarly enough the Table of Contents is at the end rather than at the beginning of the text.

The book is divided into 3 main sections. The first is on morphology and physiology. The second is entitled "Pathology" and discusses disorders of function, endocrine disorders, malformations, displacements, inflammations, and tumors. The third section is concerned with operative gynecology. While it is not specifically stated, presumably this book was written primarily for medical students. If this be true, it does not seem to the reviewer that 25 per cent of the pages should be devoted to operative gynecology—better none.

Much of the book, of course, seems to consist of standard, authentic fare, common to all textbooks. An occasional idea or fact seems unlikely if not peculiar. For example, in the nullipara, the uterus contracts during intercourse, causing the endocervical mucus to project toward the posterior cul-de-sac to meet the sperm. After intercourse, the uterus relaxes and the mucus is retracted into the endocervical canal loaded with sperm and thus giving them a boost onward and upward! —*R. R. Greene.*

THE TEXT of *Les cancers du colon*[2] is logically divided into two parts: the first deals with the more basically scientific aspects of the disease and the second deals with the therapeutic and prognostic aspects.

Roux and Carcassonne begin their work with a readable, comprehensive, and well illustrated chapter on surgical anatomy. There follows a chapter dealing with various etiologic agents.

The portion on pathologic anatomy is on the whole well executed, but it was quite obviously not written by a surgical pathologist. Although it seems to bring into focus most of the controversial problems currently under discussion, the various aspects receive a rather uneven stress. For example, 5 pages of tables are devoted to the problem of multiple cancers while only a few lines are devoted to the seemingly more practical problem of cancer cell spillage as it relates to problems of "cancer cell contamination" analogous to sterile technique.

The section further suffers in that there is insufficient correlation of pathologic findings with prognosis, although prognosis receives excellent attention at the end of the book.

It is somewhat disturbing that only 6 photomicrographs appear in the entire book and the 1 gross photograph is that of a metastasis. There are no illustrations of the average case.

All of the comments made, however, should be regarded as minor criticism of the book.

The chapter on radiologic aspects was written by an obviously enthusiastic and experienced radiologist. It is profusely illustrated with many explanatory notes, diagrams, and sketches which require at least two-thirds of almost every page.

Just as the section on radiology benefited by its having been written by a loving hand, so do the authors, who are surgeons, lavish their enthusiasm on the section dealing with the surgical aspects of colon cancer. Here again there are numerous sketches with explanatory notes, and extreme clarity and pointedness of language.

This book is especially worth while in that it avoids the "regionalism" so often found in medical writers—its international approach is obvious throughout the entire book. —*W. Newlon Tauxe.*

THE POPULAR BOOK *Clinical Biochemistry*[3] has been completely rewritten. Due to the closer integration of clinical medicine with the basic medical sciences in recent years, the elementary level used in early editions has been discarded and the authors discuss the normal aspects of metabolism and biochemical mechanisms more extensively.

All topics concerning the biochemical approach to diagnosis and management of disease are included. Theories of all the topics in the previous edition have been brought up to date along with the addition of new material on liver and kidney function; abnormalities in plasma protein; biologic significance of nucleic acids; metabolism of uric acid, porphyrin, iodine, and potassium; lipoproteins; fatty liver; acid-base balance; diagnosis of disorders in the function of the endocrine glands, especially the thyroid and adrenal; and the biochemical aspects of diet.

This book is written in a style that is easy to read and each chapter is organized into sections set off by headings in bold face type. Space is saved by giving a brief list of selected reviews and monographs at the

[1] GYNECOLOGIE; TRAITÉ POUR ÉTUDIANTS ET PRATICIENS. By Nicholas C. Louros. Translated from the Greek by Télémaque Nicoglou. 404 pages, 397 illustrations. 5.500 francs. Paris: Expansion scientifique francaise, 1955.

[2] LES CANCERS DU COLON. By Marcel Roux and F. Carcassonne, in collaboration with R. Le Canuet. 368 pages, 140 figures. 3.200 fr. Paris: Masson & Co., 1955.

[3] CLINICAL BIOCHEMISTRY. By Abraham Cantarow, M.D., and Max Trumper, Ph.D. 5th ed. 738 pages, 54 illustrations. $9.00 Philadelphia and London: W. B. Saunders Co., 1955.

end of each chapter instead of references in the text and longer bibliographies. This may be a disadvantage when the book is used as a reference. Directions are not given for performing tests and assays as they can be found in laboratory manuals. The table of contents and index are extensive.

Clinical Biochemistry is a book that will be an asset to every physician who depends on the clinical laboratory for help in diagnosis and prognosis. It will bring one up to date in this rapidly changing field. It will also be of assistance to clinical pathologists and to medical students. —*Opal E. Hepler.*

THE STATED AIM of *Chirurgie du corps thyroide*[4] (Surgery of the Thyroid Gland) is to clarify therapeutic indications, to analyze the results, and to attempt to avoid complications and pitfalls. The author adds that he intends to present in detail surgical technique, a field, according to him, too often glossed over by many writers. Without further ado, the author launches into a detailed and well illustrated description of a subtotal thyroidectomy. Of particular merit is the handling of the complications of this procedure.

A description of the clinical examination follows, and a quite interesting description of the biochemical aspects of iodine metabolism. It is perhaps this part of the book which will first become "dated," owing to the large amount of research now being done on this aspect of thyroid disease. It is noteworthy, however, that no recent work would gainsay any of the material he presents.

A long and well correlated section concerning the pathologic aspects of the diseases makes up the rest of the work.

One is mildly surprised that there is a total lack of photomicrographs. Only 5 drawings of the microscopic aspects are presented. Gross photographs are even rarer and none of these are notable for their clarity. Perhaps this is just another luxury we have come to expect, for truthfully, in reading the book, one does not sense their dearth.

The book's title indicates that it is a treatise on surgery, and thus that aspect receives particular stress. It is obvious that the author is a surgeon of wide clinical experience and that he has also a thorough command of the world's literature on the subject.

One is impressed with the honesty of approach; it is refreshing to find such statements as the frank admission, for example, that he has never seen a case of Riedel's struma.

Rather curious is the appearance of Levitt's book on the basic reading list, yet it is frequently referred to only for well deserved condemnation. (Levitt's name is consistently misspelled.)

While reading the monograph, one is constantly pleased by the excellent correlation of ideas, an aspect which holds the reader's attention from beginning to end. —*W. Newlon Tauxe.*

AS INDICATED BY THE TITLE, the 166 page monograph entitled *Pulmonary Resection for Tuberculosis*[5] deals with an evaluation of extirpative surgery for pulmonary tuberculosis.

The material that forms the basis of this evaluation is derived from two sources. During the years 1950 to 1952, Dr. Ottosen served as resident physician at the Missouri State Sanatorium in Mount Vernon, Missouri. Subsequently he returned to Denmark where he worked at the Kommunehospitalet in Aarhus. The present work is, therefore, a review of the experience available for review at the Missouri State Sanatorium (138 resections) supplemented by a smaller series of 43 resections in Denmark. The latter were performed between August of 1952 and April of 1954. These series are analyzed along the usual and customary lines being in effect compared one with the other.

Since the Missouri institution, however, uses epidural anesthesia as a routine technique, the chapter dealing with this experience is of interest.

The booklet is well written, amply illustrated, and the statistical information is presented in tabulated form. It forms a clear and factual record of the thinking as well as the performance in these two hospitals as viewed by the same person.—*Hiram T. Langston.*

THE AUTHOR of the pocket-size guide, *Counseling in Medical Genetics*,[6] has not pretended to create an exhaustive textbook concerning human genetics. Rather, he has applied his considerable experience in the field of genetic counseling to a description of the ways in which understanding of the mechanisms of inheritance and utilization of the tools of research can help the doctor to provide valid answers to the questions of his patients. He decries the tendency of busy practitioners to offer the solace that the odds against appearance of an undesirable trait or repetition of a developmental anomaly are "one in a million" and urges that they be prepared, instead, to furnish a statistical basis for the persons involved to make their own decisions regarding reproduction.

After a preliminary section outlining the problems which might confront the counselor in genetics and the basic laws underlying his advice, the author devoted a chapter to each of some 20 conditions and characteristics which he discusses in some detail. If one is surprised at the inclusion of tuberculosis and rheumatic fever, he might be equally disappointed by the lack of reference to malignant disease. Omissions are obviously necessary and must have been calculated. Compensation is partially provided by a bibliography pertinent to the material presented in the text and by a listing in the appendix of a large assortment of more or less rare diseases together with a brief statement of their probable mode of inheritance and their frequency of expression.

Previous acquaintance of the reader with the principles of genetics is a helpful prerequisite to maximal appreciation of the book. An obvious effort has been made, however, to avoid technical terms and the appendix supplies definitions of the most unfamiliar words. The style of expression emphasizes simplicity and clarity, with infrequent inclusion of formulas and other hallmarks of the statistician.

[4] CHIRURGIE DU CORPS THYROIDE. By Sylvain Blondin. 292 pages, 37 illustrations. 2.000 fr. Paris: Masson & Co., 1955.

[5] PULMONARY RESECTION FOR TUBERCULOSIS. By Poul Ottosen. 166 pages, 44 illustrations. $3.00. Aarhus, Denmark: Universitetsforlaget, 1955.

[6] COUNSELING IN MEDICAL GENETICS. By Sheldon C. Reed. 268 pages. $4.00. Philadelphia and London: W. B. Saunders Co., 1955.

The author has not intended to provide a textbook of genetics, but the beginning student will find the volume interesting supplementary reading and the professional geneticist will enjoy it as a sympathetic exposition of applied genetics. The book should well fulfill its primary purpose: to provide the practicing physician with a brief and authoritative résumé of the most frequent problems in human heredity.

—*Elizabeth Mussey.*

BASED UPON A STUDY of 396 cases of congenital heart disease, the volume entitled *Diagnosis of Congenital Heart Disease*,[7] in early chapters, contains discussions on the embryology of the blood vessels and the heart, the roentgenologic anatomy and physiology of the heart, and the technique of phonocardiography, electrocardiography, roentgenologic examination, electrokymography, cardiac catheterization, and angiocardiography.

Succeeding chapters are devoted to a thorough clinical and laboratory study of each of the important congenital cardiac malformations.

One can scarcely avoid the use of superlatives in discussing this remarkable book—it is a classic. The text is logical, clear, and concise, and the illustrations are superb. The entire work represents a condensation into one volume of the essentials of our present knowledge of congenital heart disease. No student of this subject can afford to be without it.

—*Stanley Gibson.*

A DEFINITIVE TEXT covering the entire field of the bleeding diatheses constitutes the volume entitled *The Hemorrhagic Disorders*.[8] The most important factor which raises this volume above that of just another monograph in the field is the approach to a standard nomenclature. One of the authors (M. S.) is the pioneer in this matter of nomenclature in an area notorious for the multiplicity of synonyms. He has taken a discriminating stand on the problem, and with any cooperation should accomplish much.

This work is exhaustive. A thorough groundwork of the fundamental principles of the field is developed, new or more obtuse facts are thoroughly documented, and at the same time, the text gives extensive coverage of the various aspects of clinical problems. In spite of Doctor Stefanini's specialized interest in platelets, the text is well balanced. It offers a most timely presentation of vascular factors in hemostasis, complete coverage of the coagulation and fibrinolytic mechanisms, and the first collection of all basic knowledge on the role of the platelets. The text is well indexed, and there is an appendix constituting a handbook of laboratory methods. Not only is this work of paramount interest to all who come in contact with bleeding problems, but it bids fair to become the standard text in the field. Familiarity with and access to this work are practical necessities for any well informed physician.

—*Frank R. Elliott.*

THE VOLUME ENTITLED *Peptic Ulcer; Diagnosis and Treatment*[9] is designed for the practicing physician as contrasted with the research worker, the gastroenterologist, and the surgeon, for whom, as the authors state, many excellent books directed toward their special interests are already available. The authors are well trained, competent gastroenterologists with extensive experience in the treatment of all varieties of peptic ulcer. They have succeeded admirably in their design to present to the general practitioner clear concepts of the physiology of the stomach, what is known of the etiology of peptic ulcer, and time-tested and approved methods for medical treatment. As might be expected from the senior author's long interest in the use of diet in the treatment of disease, instructions concerning the dietary treatment of ulcer are especially clear and useful. In addition to the older and well established methods of treatment by antacids, the authors provide a summary of the present status of the use of the antisecretory drugs. Their conclusion that these drugs should be used only as an adjuvant to other methods of medical treatment seems very wise. For the 10 per cent of duodenal ulcer patients who subsequently require surgical treatment, the authors have discussed the various operations that are presently available. In these recommendations, the authors have made a great effort to present a fair judgment concerning the conflicting views that are prevalent in this controversial field. This book is a safe guide and should prove of great value to the many physicians who are called upon to treat patients with gastric and duodenal ulcers.

—*Lester R. Dragstedt.*

THOUGHTFUL TABULATION and re-examination of Berman's results in 2,500 obstetrical cases form the basis of the text of *Obstetrical Roentgenology*.[10] The organization of this material into lectures for interns and residents over a number of years has resulted in a dynamic presentation of this overlapping field of obstetrics and roentgenology. For the most part the presentation concerns itself with pelvimetry, though chapters are included on pelvic classification, the fetus and the placenta. The illustrations, in the roentgenographic image, are numerous (486), and they are well executed. Dr. Berman's attitude concerning the place of the roentgenologist will, I am afraid, not be shared completely by either roentgenologists or all of his colleagues. The inclusion of specific technical factors for producing the roentgenograms serves, I believe, very little purpose in the modern x-ray department in which one would scarcely think of using low milliamperage and the long time necessary to make an obstetrical exposure. In spite of these minor points, the text is highly recommended to obstetricians and roentgenologists, especially those in a resident status.

—*R. Burns Lewis.*

[7]DIAGNOSIS OF CONGENITAL HEART DISEASE. A CLINICAL AND TECHNICAL STUDY BY THE CARDIOLOGIC TEAM OF THE PEDIATRIC CLINIC, KAROLINSKA SJUKHUSET, STOCKHOLM. By Sven R. Kjellberg, Edgar Mannheimer, Ulf Rudhe, and Bengt Jonsson. 649 pages, 581 illustrations. $22.00. Chicago: The Year Book Publishers, Inc., 1955.

[8]THE HEMORRHAGIC DISORDERS; A CLINICAL AND THERAPEUTIC APPROACH. By Mario Stefanini, M.D., and William Dameshek, M.D. 368 pages, 147 illustrations. $11.75. New York and London: Grune & Stratton, 1955.

[9]PEPTIC ULCER; DIAGNOSIS AND TREATMENT. By Clifford J. Barborka, M.D., M.S., D.Sc., F.A.C.P., and E. Clinton Texter, Jr., M.D. 290 pages, 33 illustrations. Boston: Little, Brown & Co., 1955.

[10]OBSTETRICS AND GYNECOLOGY. Edited by Claude E. Heaton, M.D. OBSTETRICAL ROENTGENOLOGY. By Robert Berman, M.D., F.A.C.S. 599 pages, 486 illustrations. $12.50. Philadelphia: F. A. Davis Co., 1955.

IN THE VOLUME *Applied Medical Bibliography for Students*,[11] William Dosite Postell has marshalled a vast amount of information, historical and practical. Part 1, made up of the 3 initial chapters, presents the highlights of medical history as reflected in the 3 types of recording: the manuscript, the book, and the journal. This considerable coverage within a span of 25 pages is of necessity undocumented; many broad statements therein serve to whet the appetite with respect to the list of "Recommended Readings" which is found as a portion of Appendix II and which presumably will support and clarify those statements. The format of each type of publication is presented and some of the stages through which each has developed are outlined. The reader is intrigued with the famous miniaturists as well as the early translators of Galen and wishes to know more about them.

Part 2, "Modern Bibliography," is a well organized discussion of the contents of a medical library including the bibliographic tools to be found there and the effective use of such tools. In this division the librarian gives the student information concerning the types of publications in the basic sciences and the specialties as they are found in the medical library, and suggestions as to how their contents can be ascertained quickly. The author has wisely abstained from attempting to introduce foreign publications in his presentation since the most common basic reference tools in the English language are the ones with which the student will first come in contact. With a reading knowledge of a foreign language he will quickly advance to the use of foreign journals as listed in the indices and to the study of foreign reference works and other pertinent publications regardless of language source.

"Methods of Bibliography" are developed in the third section. This is a valuable division for the student when he is faced with the need for surveying the literature on various subjects and with the presentation of a paper pertaining to any medical subject. The author's careful directions with respect to the compilation of references, the organization of the subject material, and the taking of notes, bespeak years of experience in advising the student concerning his reading and reference work, hours of hunting for missing or incomplete citations, and distress at the frequently quoted, but erroneous reference. The appendices indicating "Texts Referred to . . . ," "Recommended Readings," and "Study Questions" likewise reflect the author's extensive background. It is a book which should be in the library of every medical school and hospital and on the bookshelf of each young author. Library schools, editors, and publishers will likewise find it useful. —*L. Margueriete Prime.*

[11] APPLIED MEDICAL BIBLIOGRAPHY; FOR STUDENTS. By William Dosite Postell. 142 pages, 13 illustrations. $4.50. Springfield, Ill.: Charles C Thomas, 1955.

THE CONSULTING EDITOR of *The Surgical Clinics of North America*,[12] Robert Turell, has compiled an excellent symposium on diseases of the anorectum and colon. The collective articles cover the diagnosis, preoperative and postoperative treatment, surgery, and complications of the common diseases of the anorectum and colon. The authors have succeeded in concentrating and correlating theories and clinical developments. Established principles, concepts, and procedures have been well emphasized. The articles are clearly written, concise, and contain instructive plates, diagrams, and tables. This symposium will serve as an excellent refresher course for the busy surgeon as well as the casual operator. —*Harold L. Method.*

[12] THE SURGICAL CLINICS OF NORTH AMERICA. Nationwide Number. 1524 pages, 426 illustrations. Philadelphia and London: W. B. Saunders Co., 1955.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

MEDICAL RESEARCH: A MIDCENTURY SURVEY. Published for The American Foundation, New York. Vol. I. AMERICAN MEDICAL RESEARCH: IN PRINCIPLE AND PRACTICE. 765 pages. Vol. II. UNSOLVED CLINICAL PROBLEMS: IN BIOLOGICAL PERSPECTIVE. 740 pages. 2 volumes, $15.00. Boston and Toronto: Little, Brown and Co., 1955.

THE EXCEPTIONAL CHILD FACES ADULTHOOD. Proceedings of the 1955 Spring Conference of the Child Research Clinic of the Woods Schools held in collaboration with The Department of Special Education, Teachers College, Columbia University and The School of Education, the City College, New York in New York City. May 6 and 7, 1955 in 3 sessions. 114 pages.

GRUNDRISS UND ATLAS DER GYNAEKOLOGISCHEN CYTODIAGNOSTIK. By H. Smolka and H.-J. Soost. With a foreword by E. Philipp. 166 pages, 186 illustrations. DM 120.—$28.55. Stuttgart: Georg Thieme Verlag, 1956.

PHYSIOTHERAPY IN SOME SURGICAL CONDITIONS. By Joan E. Cash, B.A., M.C.S.P. (Teacher's Certificates). With a foreword by Professor F. A. R. Stammers, C.B.E., F.R.C.S. 350 pages, 24 illustrations. $5.00. Philadelphia and Montreal: J. B. Lippincott Co., 1955.

MANAGEMENT OF PAIN IN CANCER. Edited by M. J. Schiffrin, Ph.D. By Various Authors. With a foreword by Warren H. Cole, M.D. 245 pages, 10 illustrations. $4.50. Chicago: The Year Book Publishers, Inc., 1956.

O EMPRÊGO DE SEGMENTO INTESTINAL EXCLUÍDO COMO SUBSTITUTO DA BEXIGA E SUA UTILIZAÇÃO NO AUMENTO DA CAVIDADE VESICAL (trabalho experimental). By Afiz Sadi. Tese apresentada à Escola Paulista de Medicina, para o concurso à Docencia Livre de Clínica Urológica. 172 pages, 63 illustrations. São Paulo, 1955.

A PARIS SURGEON'S STORY. By Dr. Charles F. Bove, K.L.H. With Dana Lee Thomas. Foreword by Leland Stowe. 306 pages. $4.50. Boston and Toronto: Little, Brown & Co., 1956.

CAUSAL FACTORS IN CANCER OF THE LUNG. By Carl V. Weller, M.S., M.D. The Beaumont Lecture, Wayne County Medical Society, February 7, 1955. 113 pages, 20 illustrations. $3.00. Springfield, Ill.: Charles C Thomas, 1955.

PREVENTIVE MEDICINE IN WORLD WAR II. Personal Health Measures and Immunization. Vol. III. Col.

John Boyd Coates, Editor in Chief, and Ebbe Curtis Hoff, Ph.D., M.D., Editor for Preventive Medicine. 394 pages. Washington, D. C.: Office of the Surgeon General, Department of the Army, 1955.

JOINT LIGAMENT RELAXATION TREATED BY FIBRO-OSSEOUS PROLIFERATION. By George Stuart Hackett, M.D., F.A.C.S. 97 pages, 17 illustrations. $4.75. Springfield, Ill.: Charles C Thomas, 1956.

RETROLENTAL FIBROPLASIA; ROLE OF OXYGEN. Report of the Sixteenth M & R Pediatric Research Conference. 62 pages, 20 illustrations. Issued by M & R Pediatric Research Conference. 62 pages, 20 illustrations. Issued by M & R Laboratories, Columbus 16, Ohio, 1955.

LE TENDENZE ATTUALI NELLA GINECOLOGIA OPERATORIA. Luigi Cattaneo, Direttore. Relazione tenuta al XLIII congresso della Soc. Italiana di Ostetricia e Ginecologia, Roma, Settembre 1953. Estratto dal volume degli atti del congresso. Clinica ostetrica e ginecologica dell'universita di Roma. 77 pages, 43 illustrations. Fidenza: Tito Mattioli, 1955.

ANDROGENS; BIOCHEMISTRY, PHYSIOLOGY, AND CLINICAL SIGNIFICANCE. By Ralph I. Dorfman, Ph.D., and Reginald A. Shipley, M.D. 590 pages, illustrated. $13.50. New York: John Wiley & Sons, Inc.; London: Chapman & Hall, Ltd., 1956.

PATHOLOGIC PHYSIOLOGY; MECHANISMS OF DISEASE. Edited by William A. Sodeman, M.D., F.A.C.P. 2nd ed. 963 pages, 173 illustrations. $13.00. Philadelphia and London: W. B. Saunders Co., 1956.

HANDBOOK OF TOXICOLOGY. Vol. I. Acute Toxicities of Solids, Liquids and Gases to Laboratory Animals. Edited by William S. Spector. Prepared under the Direction of the Committee on the Handbook of Biological Data. Division of Biology and Agriculture, the National Academy of Sciences, the National Research Council. 408 pages. $7.00. Philadelphia and London: W. B. Saunders Co., 1956.

VIGÉSIMOSEXTO CONGRESO ARGENTINO DE CIRUGÍA. Fascículo I. Relatos oficiales. Publicado bajo de dirección del Dr. J. Alfredo Ferreira. Actas de la asociacion Argentina de cirugia. Dr. Alejandro J. Pavlovsky, Presidente. 831 pages, illustrated. Buenos Aires, 1955.

LE MESENCHIMOPATIE CHIRURGICHE; CONSIDERAZIONI CLINICHE E RICERCHE SPERIMENTALI. Dr. Pietro Li Voti, assistente e libero docente. Foreword by Prof. G. Nicolosi. Istituto di patologia chirurgica e propedeutica clinica della universita' di Palermo. 122 pages, 21 illustrations. Palermo: D. E. L. F., 1955.

ATLAS OF PLASTER CASE TECHNIQUES. By E. E. Bleck, M.D., Nellie Duckworth, and Nancy Hunter. 128 pages, 347 illustrations. $4.75. Chicago: The Year Book Publishers, Inc., 1956.

CIBA FOUNDATION SYMPOSIUM ON EXPERIMENTAL TUBERCULOSIS; BACILLUS AND HOST, WITH AN ADDENDUM ON LEPROSY. Editors for the Ciba Foundation, G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Margaret P. Cameron, M.A., A.B.L.S. Assisted by Cecilia M. O'Connor, B.Sc. 396 pages, 69 illustrations. $9.00. Boston: Little, Brown & Co., 1955.

Correspondence

ACUTE CHOLECYSTITIS FOLLOWING THE SURGICAL TREATMENT OF UNRELATED DISEASE—*A Correction.*

DR. FRANK GLENN wishes to call attention to the fact that in Table III, which appears in their paper entitled "Acute Cholecystitis Following the Surgical Treatment of Unrelated Disease" in the February issue, he and Dr. Wantz listed, in error, Cases 3 and 13 as having had a cholecystectomy. Both cases should have been listed as cholecystotomies.

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*Bonica, J.J.; and Backup, P.H.: *Northwest Med.*, 54:22, Jan., 1955.

THORAZINE*

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Smith, Kline & French Laboratories, Philadelphia

1. Karp, M.; Lamb, V.E., and Benaron, H.B.W.: Am. J. Obst. & Gynec. 69:780 (Apr.) 1955.

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

Printed by R. R. Donnelley & Sons Co., Chicago, Illinois, U. S. A.